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ACUTE VENLAFAXINE OVERDOSE WITH POSITIVE URINE IMMUNOASSAY FOR TRAMADOL – CLINICAL AND DIAGNOSTIC OVERLAP - CASE REPORT AND LITERATURE OVERVIEW

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Abstract: Objective. The overlapping of pharmacokinetics and/or the pharmacodynamics of medicines causes the occurrence of overlapping clinical syndromes and diagnostic issues, potentiated in overdoses. We report a case of severe venlafaxine poisoning where the clinical presentation and the results of rapid immunoassay test overlapped with tramadol intoxication.
Case presentation. An unconscious women with recurrent seizers, hypertension and supposed acute medication poisoning in suicidal attempt was transported to our clinic. Previously, she had been lavaged, rehydrated and treated with 20 mg diazepam iv, 40 mg furosemide at the local general hospital. Her regular tablet therapy consisted of losartan, levothyroxine, venlafaxine, occasionally tramadol.
At admission she was comatose, with isochoric normal pupils, BP 130/80 mm Hg, SaO2 86%, and recurrent episodes of seizures treated with 10mg diazepam iv, ocular clonus, hypertonus, temperature 38.9C, diaphoresis, facial hyperaemia, dark coloured urine, hyponatremia and rhabdomyolisis. The lateral flow immunoassay (AbuGnostR) was positive for tramadol, but the homogeneous enzyme immunoassay did not confirm it. After 36 hours of intensive treatment she became somnolent and reported ingestion of 2250 mg tbl Venlafaxine. The AbuGnost R test detects tramadol at cut off urine values 200ng/ml, but present cross reactivity with O-desmethyl-venlafaxine at cut off values up to 25000ng/ml. The following days she complained of muscular weakness, headaches and cognitive impairment, which lasted for more then one month after release from hospital.
Conclusion. High concentrations of venlafaxine metabolites induce false positive tramadol immunoassay (AbuGnostR) test. Overlapping clinical presentations and metabolic pathways of venlafaxine and tramadol should alert physicians when interpret rapid immunoassay test. The mandatory principle when making medical decisions should cover synthesis of critically interpreted toxicology analysis, interview data and clinical features of the poisoning, which may help to avoid misleading conclusions and improve the diagnostic and therapy decisions.
Keywords: venlafaxine, tramadol, poisoning, lateral flow immunoassay,

1.INTRODUCTION

Venlafaxine is an antidepressant acting as a serotonin and norepinephrine reuptake inhibitor and weak inhibitor of dopamine reuptake.The reported poisonings with venlafaxine showed lower toxicity compared to TCA, but higher then SSRIs The complexity of treatment decisions-making for these poisonings is associated not only with the disproportionate poisoning severity to the ingestion dose (Fischer, Unterecker, & Pfuhlmann, 2012) and overlapping clinical syndromes with other serotonin and/or norepinephrine reuptake inhibitors, but also with the necessity for rapid diagnosis in clinical practice and a high likelihood of false positives of rapid immunoassay tests (Saitman, Park, & Fitzgerald, 2014).
We report a case of severe venlafaxine poisoning which clinical presentation and rapid immunoassay test (LFIA-lateral flow immunoassay) overlapped with tramadol intoxication.

2. CASE REPORT

A middle aged women was admitted at the clinic after two prolonged episodes of seizers and supposed acute poisoning with medicines in suicidal attempt. She had a history of hypothyreosis, regulary treated with tablet (tbl) euthyrox (75 mg/day), hypertension treated with tbl losartan (50mg/day), depression treated with tbl. venlafaxine 75 mg/day and traumatic injury of the right ankle and foot treated with capsule tramadol a 50 mg occasionally. After her family found her unconscious, she was taken to the local general hospital where gastric lavage was performed and crystalloids were administered. After half an hour she had seizures lasting a couple of minutes. The second episode of seizures was associated with dramatic increase of blood pressure so 10 mg diazepam intravenously (iv) with 40 mg furosemide intramuscularly (im) were administered and she was transferred to our Clinic. During the transportation she received additional 10 mg diazepam im. because of new episode of seizures.

At admission she was comatose, with isochoric pupils, BP 130/80 mm Hg, SaO2 86% with clear lungs, soft abdomen and electrocardiogram (ECG) with sinus rhythm HR 95/min, QRS 105msec, QTc 437msec, non ischemic (ascendant) ST elevation.

Soon, she had another episode of seizures associated with more severe hypoxemia (75%) treated with diazepam 10 mg iv and gradually she developed ocular clonus, with hypertonus, increased temperature 38.9C and diaphoresis with facial hyperaemia. Urinary catheter insertion revealed dark urine.

Laboratory findings showed increased white blood counts, creatine kinase (CK), myoglobin and severe hyponatremia 111mmol/l (137-145 mmol/l referent values). Serum analysis: BUN, creatinine, glycemia, bilirubinemia, alkaline phosphatase, gamma-glutamyltransferase, calcium were in referent range during the whole hospital stay of the patient (Table 1).

Table 1. Laboratory findings during hospital stay

Parameter	Day 1	Day2	Day3	Day4	Day6	Day 8	Referent
Le x109/l	23.6	17,3	10,6	10,4	6,3	7,1	4-11
AST (U/l)	31	32	38		67	29	10-34
ALT (U/l)	20	19	22		67	46	10-45
LDH (U/l)	392	276	254		223	209	<248
Na (mmol/l)	109	120	135		137	136	137-145
K (mmol/l)	3,6	3,6	3,4		3,4	3,9	3,8-5,5
CRP (mg/l)	0,6	29,9	68,1		7,1	1,9	<6
CK (U/l)	452	525		4234	1409		24-173
CK-MB (U/l)	33			40			<25
Myoglobin (ng/ml)	351	/	277	601	227	57	10-46
Troponin (ng/l)	1,3	/	7,3	6,1	/	/	<15,6

AST-Aspartate aminotransferase, ALT- Alanine aminotransferase, LDH-Lactate dehydrogenas, CRP-C-reactive protein, CK-Creatine kinase, CK-MB- Cretaine kinase-MB

The urine screening test (LFIA-AbuGnostR-BioGnost) for tramadol was positive on initial presentation. The patient was treated with crystalloids (0,9% NaCl) with dose regime 2.5 mL/kg/h IV infusion, hypertonic sodium (according Joint European Guidelines), sodium hydrogen bicarbonate (1mmol/kg i.v), diazepam 0.20mg/kg iv, ceftriaxone 2gr/day.

After 36 hours of intensive therapy and after serum concentrations of sodium were normalised, the seizures ceased. The patient was somnolent, complained of muscular weakness, difficulties in self-standing from bed and upright standing, spasm of jaw muscles, headaches, with cognitive difficulties and disorientation. She self- reported ingestion of 30 tbl venlafaxine 75mg. The re-analysis of the firstly collected urinary sample using homogenous enzyme immunoassay HEIA (Beckman coulter AU 480) excluded the presence of tramadol and its metabolites in the patient's urine. The following days gradual normalization of consciousness occurred but the headaches and cognitive deterioration persisted. Plasma levels of myoglobin reached their maximum on the fourth day of hospitalization with parallel existence of expressed muscle weakness in the same period. Treatment with intensive hydration, bicarbonates and diuretics enabled the preservation of renal function.

Consultative examination by the neurologist on the 4th day confirmed that there were no neither focal neurologic deficit nor meningeal irritation, but also noted that the patient was confused, disoriented with difficulties in maintaining contact. During the hospital stay she presented slow regression of the parameters of rhabdomyolysis with preserved renal function, and persistent cognitive impirment.

ECG at discharge presented sinus rhythm, HR 95/min, normal P wave, QRS 85msec, QTc 407msec, isoelectric ST segment.

A month after release from hospital, due to persistent headaches, selective amnesia, confusion, anxiety and insomnia, the patient was re-examined by a neurologist who excluded organic neurological suffering and deficit. She continued the treatment at the psychiatric unit.

3. DISCUSSION

There were several reports of cross-reactivity of venlafaxine with phencyclidine using rapid immunoassays(Bond, Steele, & Uges, 2003) but our presentation was first reporting of venlafaxine with tramadol cross reactivity using rapid LFIA test in acute venlafaxine overdose (VO). The goal of presenting this case is to provide a wider clinical context when interprets urine drug test results considering overlapping clinical presentation of venlafaxine poisoning with tramadol and reassessment of the inefficacy if antidote treatment (naloxone) was used in such poisonings.

Venlafaxine (antidepressant) and tramadol (analgesic) are prescribed for different medical indication but share many similarities in chemical structure, inhibition of serotonin and nor-adrenalin reuptake and metabolic pathway(Reeves & Cox, 2008). Even more, it was found that venlafaxine present analgesic effects(Jha, Mazumdar, & Bhatt, 2006) as well as tramadol have antidepressant activity(Kalra, Tayal, & Chawla, 2008). In our case, the patient was receiving concomitant treatment with tbl venlafaxine and occasionally cap. tramadol, according medical recommendation. Poisonings with venlafaxine as well as with tramadol induce overlapping clinical features, associated with their pharmacokinetic profile.

Rhabdomyolisis is a significant clinical feature of acute poisoning with antidepressants, especially with venlafaxine(Wilson, Howell, & Waring, 2007), but it is associated with acute tramadol poisoning too(Khan, Yousef, & Errayes, 2010). The laboratory findings confirmed the development of rhabdomyolisis with more then five time increase of CK (creatine phosphokinase) at the 4th day of hospitalisation and serum myoglobin as an early marker of myotoxicity (Melli, Chaudhry, & Cornblath, 2005). Myoglobinuria was not investigated in our patient due to the unavailable diagnostic tests, although some studies have found that the absence of urine myoglobin does not exclude rhabdomyolisis9. Although, seizures are confounding factor for developing of rhabdomyolisis, the proposed underlying mechanism is direct myotoxic effects of venlafaxine6, and also of tramadol poisoning(Rahimi, Soltaninejad, & Shadnia, 2014); the cardiac source of increased CK and myoglobin was excluded with ECG and normal troponin serum concentrations in our patient.

Hyponatremia (serum Na <135 mmol/l) is a serious electrolyte disturbance associated with poisoning with new generation of antidepressants including venlafaxine and tramadol poisoning(De Picker, Van Den Eede, Dumont, Moorkens, & Sabbe, 2014) too. Patients under diuretic therapy and elderly ones are at higher risk for hyponatremia, even in regular pharmacology doses (De Picker et al., 2014). The proposed mechanism is associated with serotonin reuptake inhibition, inducing either increased release of antidiuretic hormone (ADH) or increased sensitivity to ADH implying on syndrome of inappropriate secretion of ADH(De Picker et al., 2014). VO is associated with prominent hyponatremia(De Picker et al., 2014), even more pronounced than the poisonings with other types of SSRI. Our patient presented severe hyponatremia (<115 mmol/l) according Joint European Guidelines with life -threatening neurologic features (seizures, coma). Seizures cessation after correction of hyponatremia in our case was a clinical confirmation of the electrolyte imbalance as an underlying mechanism.

Serotonin syndrome (SS) in venlafaxine overdose is well documented in literature(Abadie et al., 2015). Although there was a suspicion that a tramadol poisonings causes SS(Ryan & Isbister, 2015), more studies have shown that tramadol overdose also induces the onset of SS (Tashakori & Afshari, 2010). SS is potentially life -threatening condition, confirmed in our patient according Hunter diagnostic criteria(Dunkley, Isbister, Sibbritt, Dawson, & Whyte, 2003). After complete clinical and laboratory restitution, the patient suffered from prolonged neurologic impairment, already reported in the literature considering VO.

The overlapping pharmacokinetic profile of venlafaxine and tramadol generates false positive results in diagnostic toxicological tests, too. The false positive result for tramadol LFIA in our patient resulted from the venlafaxine metabolite, O-desmethyl-venlafaxine which has similar transition to tramadol (O-desmethyl-tramadol) inducing cross- reactivity (Allen, 2006). The HEIA test from the same urine sample was negative for tramadol because has no cross-reactivity with venlafaxine and its metabolite O– desmethyl-venlafaxine; together with self-reported venlafaxine overdose, leaded to conclusion that the positive rapid LFIA test in fact diagnosed the venlafaxine poisoning. The AbuGnost R test detects tramadol with urine cut off values 200ng/ml, but present cross reactivity with O-desmethyl-venlafaxine at cut off values up to 25000ng/ml.

We presented severe VO with self-reported ingested dose of 2250 mg. Most of the cases reported association of fatal outcome with ingested venlafaxine doses in tens of grams as a contrary to the case report of poisoning with 3 grams

venlafaxine with lethal outcome where venlafaxine plasma concentrations were verified by LC-MS/MS (Vignali, Morini, Chen, Stramesi, & Groppi, 2014). The differences in the venlafaxine metabolism is associated with CYP2D6 polymorphism which induce poor, intermediate, extensive and ultrarapid venlafaxine metabolizing phenotypes(Rolla et al., 2014). These facts should be considered when observing poisonings with ingested lower venlafaxine quantities and pay attention to the clinical signs of SS and laboratory findings.

The ingested venlafaxine dose was presented based only on patient's self reporting due to the unavailability of serum venlafaxine quantification, which is a limitations of our analysis. However, the positive data from the interview, the course of clinical presentation, the results from laboratory analysis (hyponatremia), the exclusion of tramadol as the causative agent of poisoning with toxicological analyzes and prolonged patient's cognitive deterioration, were sufficient to confirm the venlafaxine poisoning. Although the clinical presentation of venlafaxine and tramadol as well as their symptomatic treatment overlap to a large extent, the dilemma about absence of clinical improvement when use the antidotal therapy (such as naloxone) in the event of respiratory failure is a key point when treating these two types of poisonings only according to the results of the rapid tests.

4. CONCLUSION

The role of rapid immunoassay test is significant and necessary for the work of the emergency departments, taking in consideration that high concentrations of venlafaxine metabolites induce false positive tramadol immunoassay (AbuGnostRBiognost) test and overlapping clinical presentations. The mandatory principle when making medical decisions should cover synthesis of critically interpreted toxicology analysis, interview data and clinical features of the poisoning, which may help to avoid misleading conclusions and improve the diagnostic and therapy decisions.

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