Intralipid administration in case of a severe venlafaxine overdose in a patient with previous gastric bypass surgery

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ABSTRACT

This case describes a patient with a history of bariatric surgery who was admitted to our hospital with a severe venlafaxine intoxication. Due to the altered anatomy of the gastrointestinal tract, the use of oral activated charcoal and large volumes of laxatives to prevent further uptake of venlafaxine was hampered. This resulted in massive absorption and a severe serotonergic syndrome. The patient was successfully treated with intravenous lipid emulsion.

1. Introduction

Venlafaxine is an antidepressant that inhibits the reuptake of serotonin, norepinephrine and dopamine. At lower amounts up to 150 mg, venlafaxine is a selective serotonin reuptake inhibitor (SSRI). However, with higher amounts selectivity decreases and also noradrenaline and dopamine reuptake is inhibited [1].

In general, mostly mild symptoms develop after overdosing. However, overdosing with venlafaxine is considered to be more toxic than overdosing with specific SSRIs [2]. In addition, severe toxicity with CNS depression, seizures, serotonin toxicity, cardiac conduction abnormalities and death is also reported [3]. Treatment of severe intoxications consists of therapies to minimize drug uptake from the gastrointestinal tract and supportive care.

We here report a patient with a history of a gastric bypass surgery with a severe venlafaxine intoxication. Gastric bypass surgery does not seem to alter the bioavailability/absorption of venlafaxine [4]. However, due to the altered gastrointestinal tract, the use of oral activated charcoal and large volumes of laxatives to prevent further uptake of venlafaxine was hampered. This resulted in massive absorption and a severe serotonergic syndrome. The patient was successfully treated with intravenous lipid emulsion (Intralipid) to reduce free serum venlafaxine levels and enhance elimination.

2. Case report

A 31-year old female with a medical history of recent deep venous thrombosis, pulmonary embolism, gastric bypass surgery and depression was presented at the emergency department after an intended overdose with venlafaxine. In addition to venlafaxine QD 150 mg as antidepressant therapy, she also used rivaroxaban QD 20 mg.

Two and a half hours before presentation that evening, she ingested 120 extended release capsules of 150 mg venlafaxine. This made the estimated total ingested dose 18 g of venlafaxine. At the time of presentation, the patient was fully conscious with a Glasgow Coma Score of 15 and no symptoms were reported. Breathing frequency was 13 pm with a saturation of 99%. Blood pressure was 130/89 mmHg and the heart rate 117 bpm. The electrocardiogram showed sinus tachycardia, and a QTc of 508 msec. Her body temperature was 36.8 °C.

To prevent further absorption of venlafaxine, a nasogastric tube was placed for administration of an oral lavage solution (MoviPrep) and activated charcoal. While still in the emergency department, the patient developed spasms in arms and legs that were observed by her mother. On arrival, she had trismus and the activated charcoal was regurgitated. Midazolam 5 mg was administered intramuscularly. Thereafter, the patient was admitted to the intensive care unit for further observation and treatment. Oral bowel lavage was continued at a lower speed because of problems with administration, likely due to the altered...
anatomy of the gastrointestinal tract. The activated charcoal was also continued.

About five and a half hours after ingestion the patient again lost consciousness, this time accompanied by apnea. Spasms were again observed, diagnosed as a second seizure. Oxygen saturation dropped to 85% and blood pressure to 80/50 mmHg. The patient was intubated, sedated with midazolam and sufentanil and norepinephrine as a vasopressor was started.

The patient had developed a respiratory and metabolic acidosis, most likely due to lactate production and hypoventilation during apnea. Furthermore, mydriasis was observed. Additional drugs of abuse testing did not find traces other than benzodiazepines (which were administered at the emergency department). All above described symptoms, in combination with the hyperthermia that the patient developed, supported the diagnosis of a serotonergic syndrome. Activated charcoal was continued and the oral lavage solution was switched to sodium sulfate as laxative since this has a smaller volume to administer.

During the next day, two more episodes of arm and leg spasms and clamped jaws were observed. A CT-cerebrum did not show any abnormalities. The spasms were examined by a neurologist and diagnosed as generalized tonic seizures. Valproic acid was started as therapy.

Since neurological symptoms persisted, also after an additional loading dose, midazolam was started again in the second night at the ICU for a few hours. During the next day symptoms worsened. The patient developed multi organ failure (MOF) with a serum creatinine of 385 µmol/L and eGFR of 12 mL/min, ASAT and ALAT of 5621 U/L and 5760 U/L respectively, and lactate of 6.4 mmol/L. Her body temperature continued and the oral lavage solution was switched to sodium sulfate as laxative.

In addition to sodium sulfate as laxative, high ending enemas and neostigmine were started in order to empty the gastro-intestinal tract as quick as possible. At that time there was no defaecation yet. Due to the previous gastric bypass, only very small amounts of volume could enter the stomach. This limited the administration speed of the lavage solution and activated charcoal.

To cool the patient, icepacks were placed, cooled infusion solution were administered and alcohol was sprayed. Body temperature lowered in 30 min from 41 °C to 40.2 °C. Due to worsening of the symptoms and the development of multi organ failure (MOF) and shock with sinus tachycardia, oliguria and a lactate and metabolic acidosis, it was decided to administer an intravenous lipid emulsion (Intralipid) as last resort. The patient was given 120 mL (1.5 mL/kg) of the solution as a single intravenous bolus dose. Additional doses were not given since Intralipid is metabolized by the liver and the patient had hepatic failure. After the start of Intralipid, first venlafaxine blood concentrations became available. The concentration 36 h after estimated intake were extremely high with concentrations of 21,273 µg/L venlafaxine and 5760 µg/L desmethyl venlafaxine, the second being an active metabolite. Normally, sum concentrations of both above 1000–1500 µg/L are reported to be toxic. All concentrations measured are shown in Fig. 1. These extremely high concentrations supported our decision to administer the intravenous lipid emulsion.

After a bolus of 40 mg of furosemide diuresis started to improve and also finally defaecation started. The patient started to improve clinically after administration of the intravenous lipid emulsion. She showed full neurological recovery, her sinus tachycardia normalized, her creatinine levels lowered, diuresis improved and liver enzymes declined. On day 5 of admission the patient was extubated. Due to a delirium that she developed and sub febrile temperatures, she stayed a few more days at the ICU. She was discharged nine days after presentation at the emergency department.

3. Discussion

We present the first documented case of a suicide attempt with venlafaxine by a patient that previously underwent bariatric surgery. Due to the altered gastrointestinal tract, the administration of laxatives and activated charcoal to limit further absorption of venlafaxine, was severely hampered. This, in combination with the high amounts taken, resulted in a very severe intoxication and the serotonin syndrome. This was ultimately treated with administration of intravenous lipid emulsion. Shortly thereafter, the patient fully recovered.

To the best of our knowledge we could only find one other case that considers intentional overdosing in a patient with previous gastric surgery. In this case, a tricyclic antidepressant (TCA) was taken. The case describes problems with placement of an orogastric tube and also with subsequent charcoal administration. Furthermore, the authors suggest that the bypass potentially facilitated rapid absorption of the TCA. The

![Fig. 1. Measured venlafaxine and desmethyl venlafaxine concentrations over time. This figure shows the measured venlafaxine and desmethyl venlafaxine concentrations on the y-axis and the time after venlafaxine overdosing on the x-axis.](image-url)
authors state that these two factors, and in our opinion also the fact that TCAs are more toxic than SSRIs and SNRIs, may have contributed to the patients death [5].

In our case we, ultimately, used intravenous lipid emulsion to reduce venlafaxine exposure and toxicity. Lipid emulsion is a well-established antidote to prevent cardiotoxicity of local anesthetics after accidental systemic exposure. Over the last decade, several case reports have become available that also support efficacy in case of toxicity or overdosing of other lipophilic drugs, including venlafaxine [6,7]. The theory behind this is the formation of a ‘lipid sink’. The administration of a bolus of lipid emulsion results in the formation of a lipid compartment within the blood. This compartment draws tissue-bound drug off the cellular receptor site, into the plasma. There, it becomes trapped in the lipid phase [5,6].

The administration of lipid emulsion in case of overdosing may have the potential to avoid intubation. In our case, if administered earlier, it may have reversed the serotonergic toxicity earlier or maybe could have prevented it. Especially, since the ingested amount of venlafaxine was extremely high and limitation/prevention of further absorption was very difficult. Most previous cases, with similar amounts of venlafaxine taken or similar measured concentrations, have been reported to be fatal [8–10]. Surely, the use of lipid emulsions should be balanced against possible complications such as allergy, fat embolism and pancreatitis. However, in case of emergency, physicians should not be too reserved about the administration. Currently, guidelines describe lipid emulsion as a last resort option without convincing evidence for its efficacy. However, this evidence will not readily be available due to challenges of randomized controlled trials within the field of toxicology research. Moreover, it can also be argued that intravenous lipid emulsions have been an important element in parenteral nutrition used over the past 50 years. With this experience, in our opinion, the potential risks of extreme overdosing with central acting agents mostly outweighs the possible harms of administration of lipid emulsion.

Because our patients temperature dropped shortly after placement of icepacks and administration of cooled infusion solution with did not use dantrolene. However, we kept this post synaptic muscle relaxant in mind to use in case the hyperthermia would have continued. Also for dantrolene, contraindications and adverse events, mainly liver toxicity, should be kept in mind. Another option to treat the serotonin syndrome could have been cyproheptadine, an anti-histaminergic drug that also has anti-serotonergic properties and could possibly antagonize the serotonergic effects of venlafaxine [11].

4. Conclusion

Physicians should be aware of difficulties with the administration of laxatives and active charcoal in patients with previous bariatric surgery that present with an intoxication. The options to limit further drug uptake are limited in these patients. In case of extreme or life threatening overdosing of venlafaxine or other central acting agents, lipid emulsion should be used more certainly and maybe earlier in treatment. In our case, administration of Intralipid led to immediate and full recovery of our patient. We believe that the younger generation of doctors should become more familiar with the administration of this rescue therapy.

Conflict of interest

The authors have no conflict of interest to declare.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] W.D. Horst, S.H. Preshorn, Mechanisms of action and clinical characteristics of three atypical antidepressants: venlafaxine, nefazodone, bupropion, J. Affect Disord. (3) (1998) 237–254.
[2] N.A. Buckley, T.A. Faunce, Atypical antidepressants in overdose: clinical considerations with respect to safety, Drug Saf. 26 (8) (2003) 539.
[3] J. Sarko, Antidepressants, old and new. A review of their adverse effects and toxicity in overdose, Emerg. Med. Clin. N. Am. 18 (4) (2000) 637–654.
[4] C.A. Kröger, et al., Comparison of bioavailability of single-dose extended-release venlafaxine capsules in obese patients before and after gastric bypass surgery, Pharmacotherapy 27 (11) (2017) 1374–1382.
[5] H.M. Rinder, J.W. Murphy, L. Higgins, Impact of unusual gastrointestinal problems on the treatment of tricyclic antidepressant overdose, Ann. Emerg. Med. (10) (1988) 1079–1081.
[6] O. Dagtekin, H. Marcus, C. Müller, B.W. Bottiger, F. Spohr, Lipid therapy for serotonin syndrome after intoxication with venlafaxine, lamotrigine and diazepam, Minerva Anestesiol. 77 (1) (2011) 93–95.
[7] S.G. Hillyard, C. Barrera-Groba, R. Tighe, Intralipid reverses coma associated with zopiclone and venlafaxine overdose, Eur. J. Anaesthesiol. Eur. J. Anaesthesiol. 27 (6) (2010) 582–583.
[8] G.M. Boser, A. Spiller, A.M. Collins, A fatal case of venlafaxine overdose, J. Med. Toxicol. 4 (1) (2008) 18–20.
[9] M. Battista, et al., The spectrum of acute heart failure after venlafaxine overdose, Clin. Toxicol. 51 (2) (2013) 92–95.
[10] J.E. Mazur, J.D. Doty, S.S. Krygel, Fatality related to a 30-g venlafaxine overdose, Pharmacotherapy 23 (12) (2003) 1668–1672.
[11] M.M. Iqbal, M.J. Basil, J. Kaplan, M.D. Iqbal, Overview of serotonin syndrome, Ann. Clin. Psychiatry 24 (4) (2012) 310–318.