

Serotonin Syndrome Due to an Overdose of Moclobemide and Venlafaxine: Case Report and Review of the Literature

Grison-Hernando H¹, Monteil-Ganiere C^{*1}, Guitton C², Deslandes G¹, Boels D³, Bouquié R¹, Azoulay-Fauconnier C¹, Dailly E¹, Pineau A¹, Villers D², Jolliet P¹

¹ Pharmacology-Toxicology Laboratory, University Hospital of Nantes, France

² Medical Intensive Care Unit, University Hospital of Nantes, France

³ Poison Control Center, University Hospital of Angers, France

Introduction

Serotonin is a neurotransmitter produced in presynaptic neurons by hydroxylation and decarboxylation of the dietary amino acid L-tryptophan. After neuronal stimulation, serotonin is released into the intrasynaptic space where serotonin binds to postsynaptic receptors to effect neurotransmission. Presynaptic serotonin receptors function as a feedback loop to inhibit additional release. A reuptake mechanism returns serotonin to the cytoplasm of the presynaptic neuron where it is inactivated by monoamine oxidase.

Serotonin syndrome (SS) is the result of an excess of serotonin linked to taking substances which increase the quantity of serotonin in the central nervous system (CNS) [1,2]. It was demonstrated in animals that, in the SS, the level of extracellular serotonin was at least 10-fold greater than the basal level [3]. This excess of serotonin leads to an overstimulation of postsynaptic receptors in the CNS, mainly of the 5-HT_{1A} receptors, associated with hyperactivity, hyperreflexia and anxiety, and the 5-HT_{2A} type, associated with hyperthermia, incoordination and neuromuscular excitement [4].

The SS can be caused by taking an excessive quantity of just one medicine, or more often, following the simultaneous ingestion of several drugs which synergistically increase the synaptic serotonin quantity [5,6]. SS can also arise when successively taking two serotonergic drugs with an insufficiently long treatment-free interval. The majority of products concerned are antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), non-selective inhibitors, such as serotonin-norepinephrin reuptake inhibitors (SNRI), monoamine oxidase inhibitors (MAOIs), but there are also opiates and substances classed as narcotics such as cocaine and LSD [7]. The diagnosis of SS depends on clinical signs which combine consciousness disturbances, neuromuscular tone abnormalities and autonomic hyperactivity (tremor, agitation, hypertension, cardiac rhythm disorders)[4]. The presentation of SS ranges from mild symptoms to life-threatening cases where patients need to be admitted to hospital and receive appropriate care. Diagnosis criteria were proposed by several authors. The Sternbach's criteria [8] were modified by Radomski et al [9]. In 2003, Dunkley et al [10] proposed more simple criteria to evaluate serotonin toxicity. A guideline intended for health professionals, for appropriate out-of-hospital triage and initial management in patients with a suspected ingestion of SSRIs was published in 2007 by Nelson et al [11].

Several cases of SS linked to overdoses of antidepressants or other substances which potentiate serotonin have been described in the literature. However, plasma concentrations of the drugs involved are rarely available. The case presented below is a case of acute moclobemide and venlafaxine poisoning having brought about severe SS. The plasma concentrations were monitored over the six days spent in the Medical Resuscitation Unit. The initial concentrations allowed to confirm the diagnosis. The slow elimination of the drugs showed that

the duration of the SS depends not only on the medical care but also on the pharmacokinetics (half-lives) and pharmacodynamics (molecular mechanisms) properties of the drugs.

Case Report

A 52 year-old man who had already tried to commit suicide several times in the past, and who had no other medical history, was found sweating and with generalized tremors. A case of deliberate self-poisoning with medicine was suspected. The quantities which had supposedly been ingested were 40 Effexor[®] 75 mg tablets, that is to say 3 g of venlafaxine, and 30 Mocloamine[®] 150 mg tablets, that is to say 4.5 g of moclobemide, that the patient later said he had swallowed 5.5 h previously. He was transferred to hospital and suffered a bout of convulsions in transit. Upon arrival at the casualty department, the patient was feverish (42°C) and in a deep coma with a Glasgow score of 3. He presented with hypertonia of the legs and spontaneous clonus as well as with tachycardia (150/min) without associated arterial hypertension (AHT) (arterial pressure of 110/55 mm Hg). The pupils were dilated, symmetrical and rather unreactive. The electrocardiogram showed a normal sinus rhythm and there was no associated haemodynamic failure. The brain scan was normal. Initial care consisted in intubation, sedation with midazolam and administration of fentanyl. The patient was then transferred to the medical resuscitation unit, where he was given dantrolene (the results of the toxicological analyses were not known). As it was inactive on the hypertonia, dantrolene was stopped and curares were administered. He was also cooled externally.

The initial and follow-up biological tests highlighted acidosis (arterial pH: 7.33 (normal values: 7.36-7.42), PaCO₂: 54 mmHg (normal values: 36-43 mmHg), bicarbonates: 22.5 mmol/L (normal values: 24-34 mmol/L), lactates: 2.8 mmol/L (normal values: 0.6-2.4 mmol/L)); rhabdomyolysis (creatinine phosphokinase: 11,400 U/L at day 2 (normal values 0-189 U/L), myoglobin: 9,385 µg/L (normal values 28-72 µg/L)), hepatic cytolysis without hepatocellular failure (maximum at day 2: AST: 244 U/L, ALT: 77 U/L (normal values 0-40 U/L)). Renal function remained normal. The diagnosis of serotonin syndrome due to deliberate self-poisoning with a medicine associating an MAOI and an SNRI was made. The treatment consisted in maintaining sedation with benzodiazepines, without using opiates which potentiate SS –

***Corresponding author:** Catherine Monteil-Ganiere, Pharmacology – Toxicology Laboratory University Hospital of Nantes, Nantes, France, Tel: + 33 2 40 08 41 98; E-mail: catherine.ganiere@chu-nantes.fr

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fentanyl was thus stopped – the patient was given a curare. These two drugs were effective on hypertonia and clonus. The core temperature lowered rapidly. During the three following days, when the curare and sedation were stopped, clonus occurred again. So, the treatment was re-administered. On day 4, the arrest of the medications was successful. The patient was extubated on day 5 with a smooth recovery and was transferred to the psychiatric ward on day 6.

Toxicological Analyses

Method

Samples were taken for toxicological analysis 9.5 h after ingestion. Then samples were withdrawn once a day until day 6, in order to monitor the evolution of plasma concentrations.

Chromatography screening was carried out by high-performance liquid chromatography with diode array detector (HPLC-DAD) (Alliance, Waters) and by gas chromatography with mass spectrometry (GC-MS) (Agilent Technology), after liquid-liquid extraction in an alkaline mode. The drugs were identified by their spectra (UV spectrum in HPLC-DAD and mass spectrum in GC-MS) and their retention times. Quantification was then done by HPLC-DAD (Alliance, Waters) on the plasma samples taken over a period of six consecutive days. The liquid-liquid extraction used a tri-solvent mixture (trichloromethane: propanol-2: n-heptan; 60:14:26 v/v) in a base mode [12] with prazepam as internal standard. The sample volume was 2 mL of plasma. The chromatographic separation was performed on an analytical column (Symmetry C8 5 μ m 4.6 \times 250 mm, Waters) with a gradient using a mobile phase A (acetonitrile) and a mobile phase B (sodium phosphate buffer pH 3.6). Moclobemide, venlafaxine, O-desmethylvenlafaxine (ODV) and prazepam were supplied by Cerilliant Corporation (Round Rock, Texas). A calibration curve was carried out with drug-free plasma spiked at five concentration points (0.1, 0.5, 1.0, 2.0, 4.0 mg/L) for moclobemide, venlafaxine, ODV in the same chromatographic run. The method was validated according to the French accreditation committee (COFRAC), document SH GTA 04: repeatability, reproducibility, accuracy, linearity, limit of quantification. The coefficients of variation (CV) of the repeatability (five times the same day) and reproducibility (five different days) assays and the inaccuracy were below 10 %. The limit of quantification was 0.04 mg/L for the three compounds.

Results

The blood-alcohol level measured on the first blood sample was 1 g/L.

Various molecules were identified with the screening: moclobemide, venlafaxine and its active metabolite ODV, cyamemazine and midazolam. Cyamemazine, detected only in the first sample, was part of the patient's drug treatment. Midazolam was administered throughout the course of the patient's hospitalization to maintain sedation.

In the sample which was taken 9.5 h after ingestion, very high concentrations were measured for moclobemide (41.9 mg/L) and venlafaxine (5.8 mg/L) (Figures 1 and 2).

The concentration decay over time is very slow, with half-lives calculated in the patient of about 16 h for moclobemide and 48 h for venlafaxine.

The main metabolite of venlafaxine, ODV, which is pharmacologically active [13], was also highlighted and dosed. The maximum concentration was reached at day 4, with 0.9 mg/L. This

metabolite was still detectable at day 6, with a concentration of 0.1 mg/L (Figure 3).

Discussion

The concentrations of moclobemide (41.9 mg/L) and venlafaxine (5.8 mg/L) are well above therapeutic and toxic concentrations (Figures 1 and 2). Therapeutic concentrations vary between 0.5 and 1.5 mg/L for moclobemide and between 0.2 and 0.4 mg/L for venlafaxine. Concentrations considered as toxic are higher than 11.0 mg/L for moclobemide and higher than 1.0 mg/L for venlafaxine [14]. The half-lives calculated in the patient (16 h for moclobemide and 48 h for venlafaxine) are very long compared to the half-lives for therapeutic doses (moclobemide: 1 to 3 h, venlafaxine: 3 to 5 h) [14]. Figures 1-3 showed that the 3 drugs remained at high concentrations during a few days, corresponding to the duration of the hospitalization in the resuscitation unit.

The presence of serotonergic agents at high concentrations and the clinical features allowed to diagnose a SS. According to the Hunter Serotonin Toxicity Criteria [10], the spontaneous clonus observed in our patient associated with the MAOI and SSRI intoxication is predictive of a serotonin toxicity.

Management of the serotonin syndrome includes supportive care, the control of agitation, the administration of 5-HT_{2A} antagonists,

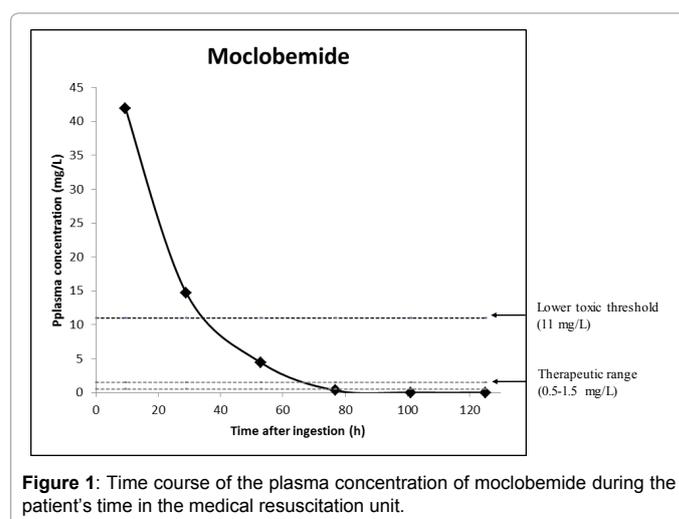


Figure 1: Time course of the plasma concentration of moclobemide during the patient's time in the medical resuscitation unit.

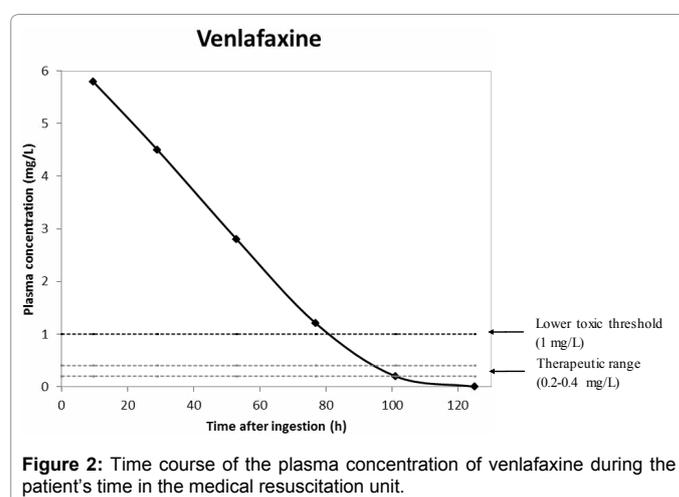
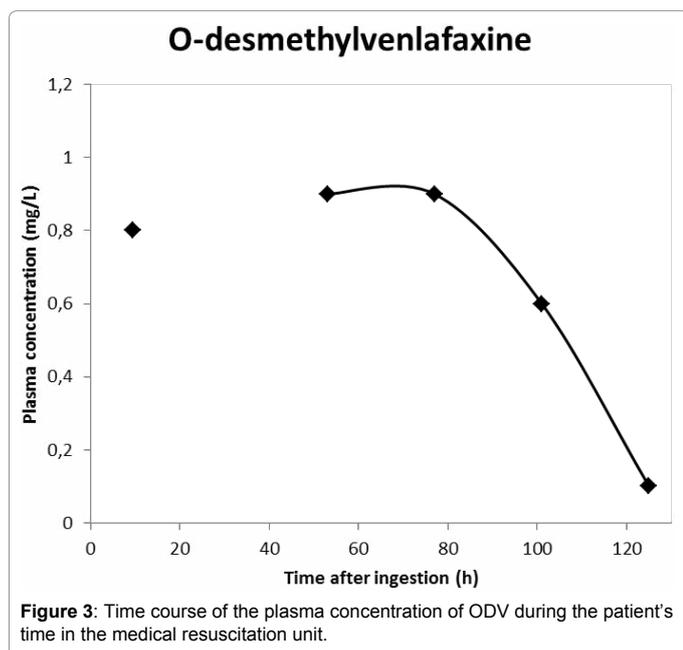


Figure 2: Time course of the plasma concentration of venlafaxine during the patient's time in the medical resuscitation unit.



the control of autonomic instability and the control of hyperthermia [1,4]. In our case, the management involved ventilation, cooling measures and administration of benzodiazepine and curare. The use of 5-HT antagonists is recommended in the literature. Cyproheptadine is the most widely prescribed in this case, although its efficacy has not been rigorously established [1,4]. This medication may only be administered nasogastrically. Chlorpromazine was also used in severe cases but should not be used if patients are hypotensive [4]. In our case, benzodiazepine associated with curare proved their effectiveness to control clonus and hypertonia.

In the literature, two cases of SS caused by acute poisonings combining moclobemide and venlafaxine have been described in Table 1 [7,15]. In the first case [7], the outcome was fatal for a woman who died 12 h after being admitted to Casualty in spite of receiving medical care. Toxicological analyses, carried out *ante-mortem*, found 24.4 mg/L of moclobemide 3 h after ingestion of 1.8 g and 0.7 mg/L of venlafaxine 2.5 h after ingestion of 1.8 g. ODV was also present, but was not quantified. Hair analysis, carried out *post-mortem*, showed that there had been regular consumption of cocaine. However, no narcotic substances were found in the blood, which indicates that cocaine had not been consumed at the time of death. In the second case [15], the quantities absorbed (3 g of moclobemide and 2.625 g of venlafaxine) are closer to those ingested by our patient, but no dosage of the medicines was carried out. The outcome was positive. Another case [16] reports a death linked to poisoning with moclobemide combined with an SSRI, namely paroxetine. The patient presented severe SS, with coma and convulsions; he died on the way to hospital. Samples taken *post-mortem*, shortly after death, highlight concentrations of 18.5 mg/L and 1.58 mg/L of moclobemide and paroxetine respectively in the blood; the quantities ingested were not known. The authors suggest that an overdose of just one of these two substances would probably not have caused such severe effects. Taking a serotonin reuptake inhibitor and a serotonin decay inhibitor (MAOI) simultaneously caused severe SS which led to the patient's death.

Moclobemide is an MAOI-type antidepressant. Pharmacokinetic and toxicokinetic studies show that moclobemide undergoes a strong

first pass metabolism, which can be saturated in the case of very high doses [17,18]. Moclobemide is completely and quickly metabolized by the liver, the metabolism route mainly involving CYP2C19. Currently, 19 metabolites have been identified in urine [18,19]. The two main metabolites in plasma are Ro 12-8095 and Ro 12-5637, the second one having a low level of activity [20]. Isbister et al showed that the metabolism of moclobemide was not saturable [18], however, an inhibition of its own metabolism (possibly by metabolites) could explain the very long half-lives observed in overdoses and in patients who have taken moclobemide repeatedly [17,18]. There is a polymorphism for CYP2C19. In poor metabolizers, the half-life is lengthened to 4 h, with a decreased plasma concentration of Ro 12-8095 [18]. Venlafaxine has not been shown to have an inhibiting effect on CYP2C19 [21].

The plasma concentration of 4.5 g of moclobemide 9.5 h after ingestion is very high (41.9 mg/L), although it is not known if this first measurement corresponds to the peak maximum concentration (C_{max}) in the patient's blood, as no previous samples were taken. After a single dose of moclobemide, the C_{max} was measured between 1.0 and 1.5 h after administering. In the case of poisonings, the T_{max} is higher and shows great variability: in 2 cases it was measured at 13 h and 4.5 h, showing a prolonged phase of absorption which could come from delayed gastric emptying, the formation of aggregates of tablets, or the saturation of absorption mechanisms [18]. In the case of poisonings, the half-life is increased in a variable way from one patient to another and is not correlated to the dose. In patients having ingested between 3 and 12 g of moclobemide, the half-lives varied between 4.3 to 10.2 h, reflecting the inter individual variability of moclobemide clearance [17,18]. In our case, the half-life was greater (16 h), whilst the ingested quantity was not higher than the one in the cases described.

Other cases of overdoses report, for ingestions of 6 and 12 g of moclobemide, maximum blood concentrations of 28 mg/L and 50 mg/L respectively [18]. Isbister et al observed the absence of major toxic effects in 33 patients having had an overdose of moclobemide alone [18]. However, three publications report cases of SS caused by moclobemide alone: Ip and Renouf [22] describe a case of SS linked to a massive ingestion of moclobemide, without any other serotonergic medicines, but with codeine which could have aggravated the serotonin toxicity; Cekmen et al [23] report a case of moclobemide overdose which led to SS with cardiac arrest, which had a successful outcome after resuscitation; Bleumink et al [24] describe a death following moclobemide overdose, combined with an apparent ingestion of whisky.

Our patient spent six days in intensive care and was ventilator-dependent for four days, which corresponds to the length of time that moclobemide was present in the blood. In the same way, Isbister et al observed a correlation between a prolonged high blood concentration of moclobemide, the evolution of clinical signs, and the length of time spent by the patient in the intensive care unit [18].

Venlafaxine is an SNRI. It is indicated for major bouts of depression and in anxiety disorders. In cases of venlafaxine overdose, severe complications have been described, such as convulsions, SS and rhabdomyolysis, which was found in our case, but also neuroleptic malignant syndrome [25-28], as well as cardiovascular disorders with tachycardia > 100/min (found in our patient), AHT and lengthened QT interval [29], which were not present in our case. Overdose with venlafaxine alone or combined with other molecules can be fatal [30].

Venlafaxine is metabolized mainly into ODV, an active metabolite, by CYP2D6. Other more minor metabolic routes involve CYP2C9, 2C19

Reference	Medicine(s)	Quantity ingested (blood concentration)				Outcome
Our case	<i>moclobemide</i> <i>venlafaxine</i>	4500 mg (41 mg/L) 3000 mg (5.8 mg/L)				favorable
[7]	<i>moclobemide</i> <i>venlafaxine</i>	1800 mg (24.4 mg/L) 1800 mg (0.7 mg/L)				death
[15]	<i>moclobemide</i> <i>venlafaxine</i>	3000 mg 2625 mg				favorable
[22,23]	<i>moclobemide</i>	high dose				favorable
[16]	<i>moclobemide</i> <i>paroxétine</i>	(18.5 mg/L) (1.58 mg/L)				death
[33]	<i>venlafaxine</i> <i>lamotrigine</i> <i>diazépam</i>	4500 mg (1.2 mg/L) 20 g (42.4 mg/L) 200 mg (0.56 mg/L)				favorable
[37]	<i>sertraline</i>	1500 mg				favorable
[38]	<i>milnacipran</i>	3000 mg (8.4 mg/L)				favorable
[39]	<i>tramadol</i> <i>citalopram</i>	therapeutic doses				favorable
[40]	<i>venlafaxine</i> <i>mirtazapine</i>	150 mg 30 mg				favorable
[41]	<i>citalopram</i> <i>oxycodone</i>	50 mg 20 mg				favorable
[42]	<i>tramadol</i> <i>oxycodone</i> <i>bupropion</i> <i>trazodone</i>	400 mg 10-20 mg 300 mg 25 mg				favorable
[43]	<i>fentanyl</i> <i>amitriptyline</i> <i>linézolide</i>	25 µg/h 25 mg 600 mg				favorable
[44]	<i>lithium</i> <i>venlafaxine</i>	therapeutic doses				favorable
[45]	<i>lithium</i> <i>paroxétine</i>	400 mg (0.63 mmol/L) 30 mg (0.693 mg/L)				favorable
[46]	électroconvulsivothérapie <i>paroxétine</i>	- 40 mg				favorable
[47]	MDMA	3 tablets				favorable
[48]	MDMA <i>moclobemide</i>	(1.7 mg/L)	(2.6 mg/L)	(1 mg/L)	(2.0 mg/L)	4 deaths
		(0.3 mg/L)	(0.7 mg/L)	(15 mg/L)	(8.7 mg/L)	
[49]	<i>méthylone</i> <i>butylone</i>	844 mg 106 mg				death

Table 1: Serotonin Syndromes reported in the literature: medicines involved, quantities ingested and corresponding blood concentrations, evolution of the patient.

and 3A4, giving inactive metabolites such as N-desmethylvenlafaxine and N,O-didesmethylvenlafaxine [13]. Studies have shown that moclobemide is an inhibitor of CYP2D6 [31], which can explain the extended half-life of venlafaxine in our case. There is a polymorphism for CYP2D6, with a poor metabolizer phenotype in 5 to 10 % of the Caucasian population [32]. Such a phenotype in our patient could have contributed to the extension of the half-life (48 h), while the usual half-life of therapeutic venlafaxine is between 3 and 5 h [14].

Few cases in the literature report the blood concentration in cases of overdose. Dagtekin et al [33] describe an SS following the ingestion of 4.5 g of venlafaxine, 20 g of lamotrigine and 200 mg of diazepam. Toxicological analysis enabled a blood concentration of 1.2 mg/L of venlafaxine and 0.3 mg/L of ODV to be measured. Another case described a blood concentration of 6.9 mg/L 5 h after ingesting 5 g of venlafaxine [32] in a female patient who presented convulsions, coma and cardiac disorders. Faced with a greatly extended half-life (12.4 h), the authors hypothesize polymorphism of CYP2D6.

SS is a set of symptoms which result in the hyperstimulation of central and peripheral serotonin receptors following a large increase in the level of serotonin in the organism after taking one or more serotonin agents [34]. Serotonin syndrome is well documented in

the literature, but it remains under-diagnosed because of the non-specificity of the symptoms; 85% of the syndromes go undiagnosed [1]. The clinical symptomatology is very variable, ranging from very mild to life-threatening [34,35]. Different mechanisms cause the increase of serotonin: the inhibition of its reuptake (antidepressants (SSRIs, SNRIs, tricyclic antidepressants), methadone, tramadol, cocaine, 3,4-methylenedioxymetamphetamine or ecstasy (MDMA)), an inhibition of its decay (MAOI-A), an increase in its synthesis (cocaine) or its release (tramadol, MDMA, L-dopa), an activation of its receptors (triptans, LSD, fentanyl, lithium) [34]. Indeed, the inhibition of certain CYP 450 can lead to a decrease in metabolism therefore an increase in the concentrations of these drugs. Thus, in multi-medicated people or patients presenting an elimination disorder, the risk of SS is higher [34,36]. Neurobiologically, studies in animals have shown, throughout the SS, an increase in noradrenaline in the anterior hypothalamus, an area of the brain which is involved in regulating body temperature. This increase causes hyperactivity of the noradrenergic system which contributes to the symptoms [37].

Serotonin syndromes have been described in the literature (Table 1) implicating various xenobiotics belonging to the different classes mentioned above, either alone or in combination. Thus, cases report serotonin syndromes with overdoses in antidepressants alone: SSRI

with sertraline [37] or SNRI with milnacipran [38], the outcome being positive in both cases. At therapeutic doses, some combinations of serotonergic medicines can cause serotonin syndrome, requiring inpatient admission to hospital, but with a mainly positive outcome: tramadol and citalopram [39], venlafaxine and mirtazapine [40], citalopram and oxycodone [41], tramadol, oxycodone, bupropion and trazodone [42], fentanyl, amitriptyline and linezolid [43]. Lithium, which causes an increase in serotonin in the brain as well as the activation of serotonin receptors, can also contribute to the onset of serotonin syndrome. Thus, cases have been described with the combination of lithium and venlafaxine [44] and lithium and paroxetine [45]. One case of SS has been described while using electroconvulsive therapy in a patient on paroxetine, with a successful outcome [46]. Concerning narcotics, MDMA is also involved, alone with a successful outcome [47] or combined with moclobemide for which four cases of death have been reported [48]. One fatal case was described following massive ingestion of two cathinones: butylone and methylene [49].

Conclusion

The case presented here shows severe poisoning with two serotonergic agents, resulting in major SS. Appropriate treatment, including ventilation, treatment of hyperthermia, sedation with benzodiazepines, halting the administering of morphine derivatives, and curarisation of the patient, led to a successful outcome. Plasma dosages enabled on the one hand to confirm the diagnosis of deliberate self-poisoning with serotonergic medications, and on the other hand to assess the scale of the poisoning, with very high concentrations, rarely observed in the literature. Toxicokinetic monitoring showed half-lives of moclobemide and venlafaxine 5 to 15 times longer than those described for therapeutic doses and enabled to explain the slow improvement of the patient's clinical state, correlated to the length of time the patient stays in the Medical Resuscitation unit. The slow elimination of moclobemide can be explained by the inhibition of its own metabolism. The inhibition of the metabolism of venlafaxine by moclobemide can explain the greatly extended half-life of venlafaxine. A polymorphism of CYP2D6 and/or CYP2C19, causing a slower metabolism of venlafaxine and of moclobemide respectively, cannot be excluded.

In this case, the toxicological analyses have provided important information. Therefore, in severe SS cases, we highly recommend a toxicological monitoring.

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