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A case of bupropion overdose: Bupropion intoxication and/or serotonin syndrome?

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INTRODUCTION

Serotonin syndrome (SS) is a life-threatening drug reaction that occurs with an increase of serotonergic activity in central and peripheral 5-hydroxytryptamine (5-HT) receptors. The main mechanism of SS is the overstimulation of postsynaptic 5-HT1A and 5-HT2A receptors. The clinical triad of SS is progressive neuromuscular hyperactivity, autonomic instability and altered mental state. It is recommended to use the Hunter Serotonin Toxicity Criteria (HSTC) to diagnose SS (Scotton et al., 2019).

Bupropion intoxication is another life-threatening clinical situation which the most common symptoms are seizures, tachycardia, agitation, psychosis, and myoclonus/tremor/hyperreflexia (Murray et al., 2020). Due to these overlapping symptoms of bupropion intoxication and SS, it is hard to differentiate them in cases of bupropion overdose.

Bupropion inhibits the reuptake of dopamine and norepinephrine in the presynaptic region, and there is no known direct effect of bupropion on serotonergic receptors in humans (Costa et al., 2019). 3 cases of SS occurring during bupropion use alone have been reported (Murray et al., 2021, Thorpe et al., 2010). On the other hand, the certain diagnosis for these cases and the likelihood of SS with bupropion as a single agent are debated (Gillman, 2010). Here, we present the case of bupropion overdose in the conundrum of bupropion intoxication and SS.

CASE

A 19-year-old female patient with bipolar disorder was admitted to the emergency room approximately 30 minutes after ingesting 30 tablets of extended-release bupropion 300 mg for suicide. On arrival, her mental state, vitals, physical and neurological examination were normal. Gastric lavage was performed. Drug particles were observed, and oral activated charcoal was administered. The creatine kinase level, lithium level, thyroid, liver and kidney function tests, electrolytes were normal, no other findings on electrocardiography except sinus tachycardia. Her brain computed tomography was completely normal.

4 hours after ingestion, her vital signs were 36.8 °C of body temperature, 154/minute of heart rate, 28/minute of respiratory rate, and 126/67 mm/Hg of body pressure. Shortly after, she had a generalized tonic-clonic seizure, 2000 mg of levetiracetam was administered intravenously. 6 hours after ingestion, her oral mucosa was dry, and she had dyskinetic movements, blurred vision, dysarthric speech, dilated pupils with preserved light reflex, increased deep tendon reflexes in all extremities, especially brisker in lower ones, myoclonus, ocular clonus, bilateral inducible achilles clonus and tremor was in neurological examination. Besides, agitation, loosening of associations, disorientation, and visual hallucinations emerged within hours. As we considered the likelihood of diagnosis as SS based on the HSTC, 12 mg cyproheptadine loading dose was perorally administered for once, and we planned to continue the treatment with 2 mg cyproheptadine every two hours until clinical improvement was achieved. However, after receiving the first maintenance dose, an internal medicine specialist evaluated the case as bupropion intoxication and 18 hours after ingestion, 20% lipid emulsion (ILE) solution as loading dose of 1.0 mL/kg and 0.25 mL/kg/min maintenance infusion of 35 minutes was administered instead of cyproheptadine. Myoclonus and ocular clonus improved, also severity of confusion decreased. 24 hours after ingestion, since the hyperreflexia, agitation, dilated pupils, tachycardia, and hypertension did not improve and her agitation, intensity of visual hallucinations, and tremor increased, also tachycardia and hypertension became more serious, we restarted cyproheptadine with the loading dose of 12 mg, and continued the treatment with 2 mg cyproheptadine every two hours. After 3 maintenance dose, 30 hours after ingestion, neurologic examination was normal, however autonomic instability continued. Finally, all signs improved by the 38th hour of ingestion and she was ready to discharge.

We obtained informed consent from the patient for the case report.

DISCUSSION

We reported a case bordering on bupropion intoxication and SS. After the bupropion overdose, the patient had multiple signs such as dyskinetic movements, generalized tonic-clonic seizure, dilated pupils, Achilles and ocular clonus, tremor, autonomic instability, confusion, rigidity, visual hallucinations, and dry mucosa. In differential diagnosis, we evaluated the patient for neuroleptic malignant syndrome (NMS), anticholinergic toxicity, thyroid crisis, SS, and bupropion intoxication. We ruled out NMS with normal CK level, lack of fever and absence of lead pipe rigidity. In this case, there are many signs of anticholinergic toxicity, such as mydriasis, dry mucosa, tachycardia, agitation, and seizures. However, typical anticholinergic signs such as fever, dry skin, genitourinary retention, and anticholinergic exposure were absent. Furthermore, hyperreflexia could not be explained with anticholinergic toxicity. Therefore, we excluded anticholinergic toxicity. Also, we ruled out thyroid crisis because of the normal level of T4.

Since bupropion intoxication and SS have overlapping symptoms, such as seizures, tachycardia, agitation, psychosis, myoclonus, tremor, and hyperreflexia (Costa et al., 2019, Murray et al., 2020), it was hard to rule out one of them. The first step is to stop the offending serotonergic medication, with supportive care to stabilise vital signs (maintenance of oxygen saturations, intravenous fluids, and continuous temperature cardiac monitoring), sedation with benzodiazepines, and managing possible seizure, for both of bupropion intoxication and SS (Murray et al., 2020, Scotton et al., 2019). Key management components for hyperthermia include sedation to reduce muscle activity and active cooling. In mild cases, supportive care is often sufficient, whereas in moderate cases, there needs to be more aggressive treatment (Scotton et al., 2019). In this case, due to the emergence of life-threatening symptoms despite supportive treatment, cyproheptadine treatment was initiated with a prediagnosis of SS. Then, cyproheptadine was interrupted and ILE, a supported treatment but not first-line for bupropion intoxication by a clinical toxicology task force in 2016 for life-threatening toxicities (refractory status epilepticus, hemodynamic instability), (Gosselin et al., 2016, Costa et al., 2019) was administered because of a prediagnosis of bupropion intoxication. However, when cyproheptadine treatment was switched to ILE, agitation, tachycardia and hyperreflexia worsened, then cyproheptadine treatment was restarted for a probable diagnosis of SS. In most reported cases of bupropion intoxication, ILE was administered for 20-30 minutes, since patients response to treatment in this time frame (Gosselin et al., 2016). In this case, the patient did not significantly response to a total of 405 mL of 20% ILE for 35 minutes. According to a review, in most of 41 patients (57.5%) with diagnosis of SS, 9 of whom were treated with cyproheptadine, had complete resolution of their symptoms within 24 hours of presentation (Mason et al., 2000). In our case, the mental and physical symptoms related to bupropion overdose, which were still persistent 6 hours after ILE treatment, improved with cyproheptadine treatment within 6 hours of drug intake. The specific improvement of myoclonus, ocular clonus, and ocular clonus symptoms with ILE treatment suggested that bupropion intoxication was an important component of the clinical entity besides SS, in this bupropion overdose case. Although symptoms totally improved after cyproheptadine administration, it may not be possible to be sure that this improvement is solely a cyproheptadine response. The probability of spontaneous resolution of symptoms within a 38-hour period with appropriate supportive treatment of SS cannot be excluded.... Since bupropion does not have a known direct serotonergic effect in humans, clinicians do not attribute the serotonergic symptoms to SS during the use of bupropion as sole agent (Costa et al., 2019, Scotton et al., 2019). Some researchers introduced SS induced by bupropion alone in retrospective bupropion-induced SS case series (Moss et al., 2019, Murray et al., 2020, Sidlak et al., 2020). In the reports multiple medication use was not excluded (Sidlak et al., 2020), and SS was not diagnosed based on the HSTC (Moss et al., 2019, Murray et al., 2020). Possible SS case reports, that is induced by bupropion, is exceptionally reported (Table 1). On the contrary, some researchers evaluated these cases Bayesian logic in operation, i.e., using the prior probability to weigh the expected outcome (Buckley et al., 2002, Gillman, 2010) and concluded that the diagnosis was bupropion intoxication. The growing tendency to accept clinical entities as SS with non-serotonergic agents contradicts HSTC (Ken Gillman, 2010), which its obligatory criteria is the 'presence of serotonergic agent' by definition.

In this case, based on the anamnesis and nation-wide prescribing system in Turkey, she was not using any medication, except bupropion for the last 10 days. Thus, bupropion is considered the sole agent that may have enhanced the clinical manifestation. Its mechanism is that bupropion increases firing of serotonergic neurons due to effect of noradrenaline on the raphe nucleus (El Mansari et al., 2008), and has indirect serotonergic activity through upregulation of vesicular monoamine transporter-2, the transporter responsible for pumping dopamine, norepinephrine, and serotonin from the cytosol into presynaptic vesicles (Foley et al., 2006). Because SS is a dose-related reaction (Costa et al., 2019), signs

Table 1. Reports of Bupropion Overdose Cases That Are In Serotonin Syndrome and Bupropion Intoxication Conundrum

Case	Case's age, gender, weight	Bupropion release aspect, dose and exposure route	Bupropion and hydroxibupropion levels	Notable clinical findings	Treatment	The duration which all findings are improved after ingestion	Remarkable points
Case 1. (Thorpe et al. 2010)	15 year-old, male, not noted weight	Sustained-release(SR), 3000 mg, peroral	At 17th hour: 280 ng/mL and 3100 ng/mL	Generalized tonic clonic seizure, visual hallucination, mydriasis, dry mucosa, rigidity, clonus in lower extremities	Supportive treatment with a total of 2 L intravenous hydration, total of 8 mg of intravenous lorazepam	36 hours	Cyproheptadine has not been administered. Intravenous 2 mg of physostigmine was administered, but not be observed no improvement.
Case 2. (Murray et al. 2021)	14 year-old, male, 73 kg	Immediate-release (IR), 2250 mg, peroral	At 3rd day: 15 ng/mL and 960 ng/mL	Status epilepticus, mydriasis, inducible clonus, ocular clonus, autonomic instability, confusion	Cyproheptadine was adminestered 8 mg for initial dose and two times 4 mg every 5 hours for maintanence via nasogastric tube, patient was intubated, loading dose of levetiracetam was adminestered.	72 hours	SS was diagnosed two days after ingestion, thus cyproheptadine was started in 2nd day.
Case 3. (Murray et al. 2021)	19 year-old, female, 67 kg	Extended-release (XL), 7950 mg, peroral	At 14th hour: 967,4 ng/mL and 3310 ng/mL	Dyskinetic movements, mydriasis, visual hallucinations, supraventricular tachycardia, QT prolongation, inducible clonus, generalized seizure, hyperthermia (39.3 °C)	Cyproheptadine was adminestered 12 mg for initial dose and three times 8 mg for maintanence via peroral (maintanance period is not indicated), Patient was intubated, i.v. lorazepam was adminestered.	37 hours	Cyproheptadine initiation time is not indicated.
Case 4. The present case	19 year-old, female, 50 kg	Extended-release (XL), 9000 mg, peroral	Not measured as a limitation, bupropion ingestion was confirmed with the nation-wide prescribing national system and reliable history.	Dyskinetic movements, generalized tonic clonic seizure, mydriasis, achilles clonus, ocular clonus, tremor, autonomic instability, confusion, rigidity, visual hallucinations, dry mucosa	Cyproheptadine was adminestered 12 mg for initial dose and eight times 2 mg every two hours for maintanence via peroral	38 hours	Although cyproheptadine was started at the 8th hour, appropriate treatment was delayed by starting ILE and stopping cyproheptadine treatment.

of bupropion intoxication and SS may occur together in case of bupropion overdose.

The use of cyproheptadine, which blocks 5-HT1A and 5-HT2 receptors, is especially recommended to treat SS in severe cases because of its beneficial effect for SS signs (Prakash et al., 2019, Scotton et al., 2019) despite of low-quality evidence for SS (Jacobs et al., 2020). In this case, ILE was administered with prediagnosis of bupropion intoxication; however, neurological symptoms except myoclonus and ocular clonus did not improve. Moreover, since cyproheptadine is a lipophilic drug (Gunja et al., 2004), ILE might have adversely affected cyproheptadine response or caused delay in response by inhibiting the absorption of cyproheptadine. Because differentiating bupropion intoxication and SS is a serious challenge, choosing the proper treatment, ILE or cyproheptadine, is complicated. In a case like this, when the symptoms of bupropion intoxication have partially subsided with ILE, it is possible to consider that the remaining neuropsychiatric symptoms may be related to serotonin syndrome. In such cases, the administration of cyproheptadine after ILE may provide additional benefits.

While there may be limited evidence regarding the serotonergic effects of bupropion, the fact that some of the neuropsychiatric symptoms of bupropion intoxication overlap with SS symptoms, and that some of these symptoms persist after ILE therapy but improve after the administration of cyproheptadine, suggests the possibility of serotonergic effects of bupropion. Based on this, further research into the presence of bupropion's serotonergic effects should be continued through in vivo and in vitro studies.

As a limitation, we could not perform plasma level of bupropion and urine toxicology due to absence of test kits on the arrival of the patient. Though, the level of bupropion cannot decisively differentiate bupropion intoxication and SS.

CONCLUSION

Due to the many overlapping signs of bupropion intoxication and SS, differentiating them is a conundrum. Because SS is a dose-related reaction, signs of SS can occur in case of bupropion overdose besides signs of bupropion intoxication if it is assumed that bupropion has serotonergic effect. Supportive care, which includes stabilizing vital signs and sedation, is the first step approach to both bupropion intoxication and SS. Cyproheptadine and ILE are both adjunctive therapies. Since the use of ILE with the diagnosis of bupropion intoxication may reduce the benefit of cyproheptadine (a lipophilic drug), which is a treatment choice for SS, it is important to make a careful differential diagnosis of bupropion intoxication and SS. While ILE reduces the symptoms of bupropion intoxication, cyproheptadine may be beneficial for residual symptoms. Early treatment is essential for shorter duration of symptoms.

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