Toxicology Reports 8 (2021) 1846–1848

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Escitalopram, bupropion, lurasidone, lamotrigine and possible vortioxetine overdose presented with serotonin syndrome and diffuse encephalopathy: A case report

Suthimon Thumtecho [a], Sorawit Wainipitapong [b,*], Suchai Suteparuk [a]

[a] Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, the Thai Red Cross Society, Bangkok, Thailand
[b] Department of Psychiatry, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, the Thai Red Cross Society, 1873 Rama IV Road, Pathumwan, 10330, Bangkok, Thailand

ARTICLE INFO

Handling Editor: Dr. Aristidis Tsatsakis

Keywords:
Escitalopram
Bupropion
Lurasidone
Lamotrigine
Serotonin syndrome
Encephalopathy

ABSTRACT

Background: Psychotropic drugs can cause neurological effects when overdosed. This study reports a case of psychotropic drugs overdose presenting with serotonin toxicity and encephalopathy.
Case presentation: A 20-year-old female with major depression presented with agitation 3 h after an overdose on multiple medications. Her current medications were vortioxetine, lamotrigine, lurasidone, and bupropion (extended-release). Vital signs showed hyperthermia and tachycardia. Neurological examination was remarkable for mydriasis and hyperreflexia with inducible ankle clonus. The electrocardiography showed sinus tachycardia with QTc 480 ms. Twelve hours later, she became obtunded and developed subcortical myoclonus. The electroencephalogram demonstrated a diffuse encephalopathy pattern without epileptic activities. She was diagnosed with serotonin syndrome based on Hunter Serotonin Toxicity Criteria. Myoclonus and abnormal vital signs resolved within hours after cyproheptadine administration, but she remained unconscious for 3.5 days. Urine drug screening was positive for benzodiazepines and metabolites, lamotrigine, escitalopram, and hydroxybupropion. This suggested she had overdosed on escitalopram which had been previously prescribed. Unfortunately, vortioxetine and lurasidone could not be detected by our current facilities.
Conclusion: This case exhibited serotonin syndrome and encephalopathy from overdose of multiple psychotropic agents. Her prolonged depressed consciousness could be explained by the half-life of the drugs and possible drug interactions.

1. Background

Multiple drug overdose is common among suicidal patients, and their history of the ingested toxins is often unclear. Common drugs used in intentional overdose in Thailand include psychotropic agents and analgesics [1]. Many psychotropic drugs cause neurological effects when overdosed. Herein, we report a case of multi-drug overdose presenting with prolonged duration of altered consciousness, inducible clonus, and hyperreflexia which may be caused by serotonin toxicity and the psychotropic effects of the drug itself.

2. Case presentation

A 20-year-old female with major depression ingested a handful of medications. Three hours later, she was discovered unconscious and brought to the Emergency Department (ED). Her current prescriptions were vortioxetine, lamotrigine, lurasidone, and bupropion (extended-release). A bag of medications was found at her room. Escitalopram was identified among the medications inside the bag, but not vortioxetine.

At the ED, she was agitated with alternating intervals of drowsiness. Her vital signs were: body temperature 38 °C, regular heart rate 150 beats per minute (bpm), blood pressure 108/62 mmHg, respiratory rate 24 breaths per minute, and oxygen saturation 98 % at room air.

Her pupils were 5 mm in diameter, and reactive to light without nystagmus or opsoclonus. Remarkable findings on neurological examination included hyperreflexia in both lower extremities with inducible ankle clonus. Bowel sounds were hyperactive. Her skin was dry and flushed. Post-urinary catheterization residual urine was 700 mL. Initial

* Corresponding author.
E-mail address: sorawit.w@chula.ac.th (S. Wainipitapong).

https://doi.org/10.1016/j.toxrep.2021.11.003
Received 10 February 2021; Received in revised form 15 August 2021; Accepted 4 November 2021
Available online 6 November 2021

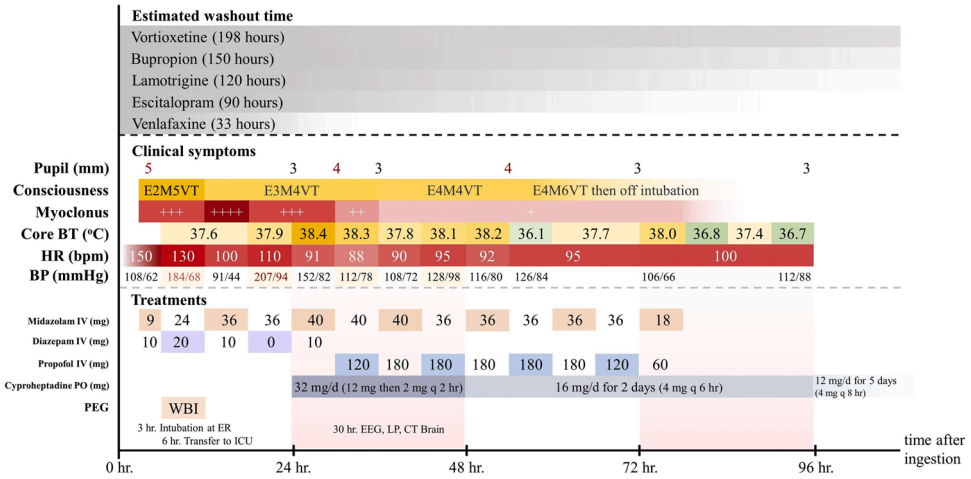

Fig. 1. Clinical manifestations, treatment and estimated wash-out time of the ingested drugs after overdose.

laboratory results, acetaminophen levels, and salicylate levels were unremarkable. The electrocardiography (ECG) showed a sinus rate of 150 bpm with a QRS interval of 80 ms and a corrected QT (QTc) interval of 480 ms. Urine drug screen was negative for amphetamine, marijuana, ketamine, cocaine, and opioids.

She was intubated for airway protection, gastric aspiration and whole-bowel irrigation (WBI). The gastric content revealed yellowish fluid (similar to both vortioxetine and lamotrigine tablets). The patient was transferred to the Intensive Care Unit (ICU) for close monitoring. She became more obtunded and developed multiple episodes of subcortical myoclonus at 12 h post-ingestion. An electroencephalogram (EEG) revealed a diffuse encephalopathy pattern without any epileptiform discharges. The computerized tomography of the brain and cerebrospinal fluid profile were normal. Large doses of diazepam (40 mg/d), midazolam (4−6 mg/h), and propofol (20−30 mg/h) were needed to control myoclonus. WBI was continued for one day until the patient delivered clear rectal effluent.

Twenty hours after ingestion, her blood pressure became 200/110 mmHg. Her temperature remained at 38−39 °C. The myoclonus and hyperreflexia persisted. Based on the Hunter Serotonin Toxicity Criteria, she was diagnosed with moderate to severe serotonin syndrome [2,3]. Cyproheptadine was initiated with a loading dose of 12 mg then 2 mg orally every 2 h for 24 h before tapering. Myoclonus resolved within hours after administration. We continued cyproheptadine for a week due to the long elimination half-life of bupropion (active metabolite 25 h) [4], escitalopram (27−32 h) [5], and vortioxetine (66 h) [6] (Fig. 1).

The clinical course was complicated by aspiration pneumonia and rhabdomyolysis with creatine kinase reaching 14,965 mg/dL before improving after supportive therapy. ECG showed resolution of QTc prolongation with no evidence of QRS widening.

The lamotrigine level at 3 h post-ingestion was 18.9 ng/dL (3−14 ng/dL) and reduced to 8.3 ng/dL after 24 h. Urine drug screening was positive for midazolam, diazepam and its metabolites, lamotrigine, escitalopram, and hydroxybupropion. Clinical manifestations and laboratory findings suggested she had overdosed on escitalopram which had been discontinued by her psychiatrist 2 weeks earlier. Vortioxetine and lurasidone could not be detected by our current facilities, so their ingestion remained unproven.

She became fully conscious 3.5 days after ingestion and was transferred to a psychiatric ward. Information about the overdosed medications was limited by her retrograde and anterograde amnesia. She received electroconvulsive therapy, psychotherapy, and venlafaxine before being discharged after a month of inpatient treatment.

3. Discussion

Serotonin syndrome is a potentially fatal adverse reaction that may be caused by therapeutic use, intentional overdose, or drug interactions that elevate synaptic serotonin [7]. The patient's initial manifestations met the Hunter serotonin toxicity criteria in terms of inducible clonus, hyperreflexia, hyperthermia, and agitation. Sedative use was immense before cyproheptadine initiation, which helped confirm the serotonergic origin of the symptoms [8]. The syndrome might be attributed to serotonergic drug overdose together with bupropion, which, despite lacking direct serotonergic activity itself, can contribute to serotonin toxicity [9]. Although escitalopram or vortioxetine (a novel serotonergic antidepressant) alone rarely causes serotonin syndrome [10], the product labels suggest potential toxicity if used with other serotonergic agents or drugs that inhibit their metabolism [5,6,11]. Additionally, concomitant use of bupropion, a strong cytochrome P450 2D6 inhibitor, and vortioxetine, extensively metabolized by this cytochrome, could lead to serotonin syndrome [10]. Unfortunately, the overdose of vortioxetine was questionable due to limited history and laboratory detection. Although escitalopram is partly metabolized by CYP2D6 [5], no interaction or cases of serotonin syndrome have been reported when concomitantly used with bupropion.

Apart from serotonin toxicity, the diffuse encephalopathy in this patient could also be explained by direct effects of the ingested drugs on the brain, namely, central anticholinergic toxidrome from bupropion [12], and neuroleptic malignant syndrome (NMS) from lurasidone [13]. Symptoms of anticholinergic toxidrome were present in our case, including flushing, urinary retention, hypertension, tachycardia, and mydriasis [14]. NMS, while possible, was less likely because the patient did not portrait any muscle rigidity.

In this patient, encephalopathy (presenting as altered sensorium) remained for the next 3.5 days before she became fully conscious, despite the dramatic resolution of abnormal vital signs and movement. This could be a result of the sedative effects of the overdosed drugs, the high dose of sedatives used during the first two days of hospital treatment, the long half-life of the drugs [4–6] and the possible drug interactions that alter their metabolism. Cyproheptadine might have also contributed to the central anticholinergic effect later in the course, but cyproheptadine-induced anticholinergic toxicity is less common in adults compared to pediatric populations according to prior case reports [15].

Lamotrigine overdose can resemble serotonin syndrome in terms of altered consciousness, tremors, myoclonus, and hyperreflexia [16,17]. Two cases in a case series met the Hunter criteria with a single lamotrigine overdose, which may be explained by its serotonin reuptake mechanism, although the lamotrigine level was not reported [18]. The

level in our patient (18.9 ng/mL) was slightly higher than the therapeutic range. In a previous systematic review, less than 20 ng/mL of lamotrigine has been reported to cause serious complications such as seizures [16] and could explain some degree of the patient's encephalopathy.

The limitation of our study was the qualitative and quantitative analysis of drugs. The patient's history of the drugs ingested was also limited. Detection of newer psychotropic agents such as vortioxetine should be implemented.

4. Conclusions

This case demonstrated serotonin syndrome and encephalopathy from a multiple psychotropic agents overdose. EEG should be performed in the presence of an altered consciousness and abnormal movement. Clinicians should look for specific presentations of a range of medications in suicidal patients, because drugs other than the current prescription may have been ingested.

Conflict of Interest

The authors declare no conflict of interest.

Authors' contributions

ST drafted the manuscript. ST, SW and SS revised, edited, read, and approved the final manuscript.

Ethical approval

This report was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Thailand. The report was [2–18] used with permission and informed consent of the patient.

Acknowledgements

The authors thank Michael D. Ullman, a Medical Manuscript Editor from their faculty, and Dr. Yanin Thipakorn from Department of Psychiatry, for editing a draft of the manuscript. Moreover, the authors would like to thank all hospital staff especially ICU nurses and doctors who deliver the best care to the patient and to psychiatrists who kindly remind the patient of the reason to keep living.

References

[1] W. Wananukul, C. Sriapha, A. Tongpoo, U. Sadabthammarak, S. Wongvisawakorn, S. Kaojarern, Human poisoning in Thailand: the Ramathibodi Poison Center's experience (2001–2004), Clin. Toxicol. 45 (2007) 582–588.
[2] E.J.C. Dunkley, G.K. Isbister, D. Sibbritt, A.H. Dawson, I.M. Whyte, The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity, QJM 96 (2003) 635–642.
[3] E.W. Boyer, M. Shannon, The serotonin syndrome, N. Engl. J. Med. 356 (23) (2009) 2437, 7.
[4] Product Information: WELLBUTRIN(R) Oral Tablets, Bupropion HCl Oral Tablets, GlaxoSmithKline (per FDA), Research Triangle Park, NC, 2011.
[5] Product Information: LEXAPRO(R) Oral Tablet, Oral Solution, Escitalopram Oxalate Tablet, Oral Solution, Forest Pharmaceuticals, Inc, St. Louis, MO, 2005.
[6] Product Information: TRINTELLIX Oral Tablets, Vortioxetine Oral Tablets, Takeda Pharmaceuticals (per FDA), Deerfield, IL, 2016.
[7] B. Arora, N. Kannikeswaran, The serotonin syndrome—the need for physician's awareness, Int. J. Emerg. Med. 3 (4) (2010) 373–377, 20.
[8] W.W. McDaniel, Serotonin syndrome: early management with cyproheptadine, Ann. Pharmacother. 35 (7–8) (2001) 870–873.
[9] B. Murray, J. Carpenter, C. Dunkley, T.P. Moran, E.A. Kiernan, T. Rianprakaisang, et al., Single-agent bupropion exposures: clinical characteristics and an atypical cause of serotonin toxicity, J. Med. Toxicol. 16 (1) (2020) 12–16.
[10] G. Chen, A.-M. Højer, J. Areberg, G. Nomikos, Vortioxetine: clinical pharmacokinetics and drug interactions, Clin. Pharmacokinet. 57 (2018) 673–686.
[11] M.T. Huska, G. Catalano, M.C. Catalano, Serotonin syndrome associated with the use of escitalopram, CNS Spectr. 12 (2007) 270–274.
[12] F. Jepsen, J. Matthews, F.J. Andrews, Sustained release bupropion overdose: an important cause of prolonged symptoms after an overdose, Emerg. Med. J. 20 (6) (2003) 560–561.
[13] M. Lee, D. Marshall, S. Saddichha, Lurasidone-associated neuroleptic malignant syndrome, J. Clin. Psychopharmacol. 37 (5) (2017) 639–640.
[14] B. Mégarbane, Drug-induced encephalopathy, in: R.D. Stevens, T. Sharshar, E. W. Ely (Eds.), Brain Disord. Crit. Illn., Cambridge University Press, Cambridge, 2013, pp. 329–343.
[15] B.S. Blaustein, T.J. Gaeta, J.R. Balentine, M. Gindi, Cyproheptadine-induced central anticholinergic syndrome in a child: a case report, Pediatr. Emerg. Care 11 (4) (1995) 235–237.
[16] B. Alyahya, M. Friesen, B. Nauche, M. Laliberté, Acute lamotrigine overdose: a systematic review of published adult and pediatric cases, Clin. Toxicol. (Phila. Pa) 56 (2018) 81–89.
[17] A. Alabi, A. Todd, A. Husband, J. Reilly, Safety profile of lamotrigine in overdose, Ther. Adv. Psychopharmacol. 6 (2016) 369–381.
[18] P.W. Moore, J.W. Donovan, K.K. Burkhart, D. Haggerty, A case series of patients with lamotrigine toxicity at one center from 2003 to 2012, Clin. Toxicol. (Phila. Pa) 51 (2013) 545–549.