Journal of Acute Medicine 9(4): 189-193, 2019
DOI:10.6705/j.jacme.201912_9(4).0005
Case Report

Successful Resuscitation of a Young Girl Who Drank Rivastigmine With Respiratory Failure

Nai-Hui Lin[1], Yu-Jang Su[1,2,3,*], Hsiu-Wu Yang[1], Hsin-Tang Chen[1]

[1]Department of Emergency Medicine, Mackay Memorial Hospital, Taipei, Taiwan
[2]Poison Center, Department of Emergency Medicine, Mackay Memorial Hospital, New Taipei City, Taiwan
[3]Department of Medicine, MacKay Medical College, New Taipei City, Taiwan

Rivastigmine is a non-competitive reversible inhibitor of acetylcholinesterase which is approved as one of the first-line treatment options for Alzheimer's disease. We present the case of a 33-year-old woman with acute cholinergic syndrome secondary to deliberate rivastigmine poisoning. The patient presented at the emergency department (ED) with drowsy consciousness, dizziness, vomiting, diarrhea, sweating, and hypertension (171/103 mmHg). At the scene, an empty bottle of Rivast 120 mL/Bot, containing rivastigmine 2 mg/mL, was found beside the patient. Two hours later, we noted bronchorrhea and persistent salivation along with drowsiness, agitation, fatigue, incontinence, and limbs paralysis. A notably low serum cholinesterase level (651 U/l) was identified. Acute cholinergic syndrome secondary to rivastigmine intoxication was diagnosed. Endotracheal intubation with ventilator support was required due to respiratory failure. Atropine (0.5 mg intravenous injection) was administered. She was subsequently admitted to the intensive care unit for further care. Extubation was performed on the third day. The patient insisted on being discharged on the second day after extubation, and after administration of a total of 11 mg of atropine, no signs of either intermediate syndrome or delayed polyneuropathy were noted. rivastigmine, an acetylcholinesterase inhibitor, can precipitate an acute cholinergic crisis in cases of intoxication. Typical clinical features of cholinergic excess include increased secretions in the airway and oral cavity, miosis, diarrhea, anxiety, twitching, bronchoconstriction, convulsions, confusion, and gastrointestinal and muscular cramps. The treatment for acute cholinergic crisis is administration of atropine alone or in combination with an antidote to the cholinesterase inhibitor (such as pralidoxime). Patients often recover well with atropine supplements and optimal supportive care.

Key words: *rivastigmine, acetylcholinesterase inhibitor, toxicity, cholinesterase activity*

Introduction

Rivastigmine is a non-competitive reversible inhibitor of acetylcholinesterase which is approved as one of the first-line treatment options for Alzheimer's disease. We present the case of 33-year-old woman with acute cholinergic syndrome secondary to deliberate rivastigmine over-dosage. Aggressive treatment at emergency department (ED) and intensive care unit (ICU), she was survived without sequelae. Acute cholinergic syndrome due to rivastigmine poisoning is rarely observed in the ED. Emergency physicians should be aware of the signs and symptoms of acute cholinergic syndrome and the presence of its toxidromes. In the PubMed database search, there are only six articles reporting rivastigmine poisoning, and we also review the literatures.

Received: January 8, 2019; Revised: February 18, 2019; Accepted: March 28, 2019.
*Corresponding author: Yu-Jang Su, MD, Department of Emergency Medicine, Mackay Memorial Hospital, No. 92, Sec. 2, ChungShan N. Rd., Taipei City 104, Taiwan. E-mail: yjsu.5885@mmh.org.tw

Case Report

A 33-year-old woman presented at our ED with complaints of dizziness, nausea, vomiting, and sweating of an hour. The patient's friend informed the emergency physician (EP) that there was an empty bottle of Rivast 120 mL/Bot, containing rivastigmine 2 mg/mL beside the patient (Fig. 1) The patient claimed to have not taken any other drug or alcohol. She experienced dizziness and vomiting for one hour after she drank the bottle of Rivast. She had also developed diarrhea and sweating, after which her friend sent her to the ED. The patient has a history of depressive episodes, without regular outpatient department follow-up. Her vital signs were: blood pressure, 171/103 mmHg; pulse rate, 150 beats/min; respiratory rate, 19 breaths/min; temperature, 36.2°C; and oxygen saturation, 100%. On arrival, she was drowsy and had a Glasgow Coma Score of 11 (E3M5V3). An intravenous fluid was administered and gastric lavage was performed. One gram per kilogram of bodyweight of activated charcoal was applied via nasogastric tube. Electrocardiogram showed sinus tachycardia. Blood tests revealed hemoglobin, 17.2 g/dL; white blood cell count, 36,200/μL; and platelet count, 389,000/μL. Arterial blood gases, electrolytes, liver and renal function tests, and cardiac markers were normal. Urine examination revealed the presence of antidepressants (> 1,000 ng/mL), amphetamines (> 500 ng/mL), methamphetamines (> 500 ng/mL), and Benzodiazepines (> 300 ng/mL). Plasma cholinesterase level was 651 U/L (reference range: 4,900–11,900 U/L). Acute cholinergic syndrome secondary to rivastigmine poisoning was diagnosed. One hour after her arrival at the ED, the patient began to present with bronchorrhea, apparent Kussmaul's respiration, persistent salivation, drowsiness, agitation, fatigue, incontinence, and limbs paralysis. Endotracheal intubation was performed due to respiratory failure. Atropine (0.5 mg) was administered intravenously. Subsequently, the patient was admitted into the medical ICU for further care. Atropine sulfate was given intravenously to treat the hypersecretion. After administration of a total of 11 mg of atropine, there was a resolution of the bronchorrhea and salivation on the second day, and extubation was performed on the third day after arrival in the ED. A psychiatric consultation was conducted due to persistent depressive disorder, and the patient was discharged, against medical advice, 4 days later.

Fig. 1. The patient's friend informed the emergency physician that there was an empty bottle of Rivast 120 mL/Bot, containing rivastigmine 2 mg/mL, beside the patient.

Discussion

Rivastigmine is an acetylcholinesterase inhibitor which was approved by the Food and Drug Administration as a first-line treatment for dementia.[1,2] Rivastigmine is a transient and slow reversible dual inhibitor of acetyl and butyryl cholinesterase.[3] Anticholinesterase agents share a common mechanism of action but come from two different chemical classes: the derivatives of phosphoric, phosphorothioic, phosphorodithioic, and phosphonic acids (organophosphates), and those of car-bamic acid (carbamates).[4] Unlike organophosphates, which bind irreversibly, and carbamates, which bind reversibly for 8–10 hours, rivastigmine binds to acetylcholinesterase for only 4–6 hours. "Pseudoirreversible" enzyme inhibition has also been used to describe the mechanism of action of rivastigmine because the duration of inhibition of acetylcholinesterase (to 4–6 hours), induced by rivastigmine is longer than its half-life (to 1 hour).[5,6]

In the literature review, only six cases of rivastigmine overdose have been reported (Table 1).[2,7-11] Two of them present with rivastigmine overdose through the gastrointestinal (GI) tract, and the others are through skin absorption. The oral form of rivastigmine poisoning is associated with a higher incidence of GI side effects.[3] Brvar, et al. presented a case of a 59-year-old man who took 48 tablets of Exelon® (288

Table 1. List of six cases with rivastigmine intoxication

	1	2	3	4	5	6
Journal	*Clinical Toxicology (Phila)*[7]	*Emerg Med J*[8]	*Hum Exp Toxicol*[9]	*Am J Emerg Med*[10]	*Curr Drug Saf*[2]	*Clinical Toxicology (Phila)*[11]
Year	2005	2006	2009	2011	2012	2017
Country	Slovenia	Turkey	United States	Korea	Sweden	Japan
Age (years)	59	38	80	70	87	91
Gender	Male	Male	Female	Female	Male	Female
Exposure routes	Oral	Oral	Transdermal	Transdermal	Transdermal	Transdermal
Doses	288 mg	90 mg	85.5 mg	138 mg	114 mg	180 mg
Symptoms	Comatose, seizures, hypertension miosis, nystagmus, salivation, bronchial secretions	Dizziness, nausea, vomiting, sweating, salivation	Lightheadedness, vomiting, diarrhea, and bilateral lower extremity muscle pain	Sweating vomiting, diarrhea, abdominal pain	Nausea, vomiting, acute renal failure	Hypertension, vomiting, miosis, sweating
Treatment	6 mg atropine IV	3 mg atropine IV	1 g of pralidoxime, and remove patches	Remove patches	Remove patches	Remove patches
Outcomes	Symptoms disappeared 23 hours later	Symptoms disappeared 16 hours later	Significant improvement after 30 minutes, discharged 3 days later.	Symptoms disappeared 4 days later	Mortality	Symptoms disappeared 17 hours later

IV: intravenous injection.

mg of rivastigmine) intentionally. He experienced somnolence, vomiting, miosis, nystagmus, excessive salivation, and increased bronchial secretions.[7] Sener and Ozsarac described another case of a 38-year-old man who complained of dizziness, nausea, vomiting, sweating, and salivation, 2 hours after ingesting 15 pills of his grandfather's medication.[8]

In our case, the toxidrome of acute cholinergic syndrome with respiratory failure occurred after drinking one bottle of rivastigmine. These compounds inhibit acetyl-cholinesterase enzymes, thereby causing an elevation in the levels of the neurotransmitter, acetylcholine.[4] Clinical signs of intoxication include increased secretions, bronchoconstriction, miosis, GI cramps, diarrhea, bradycardia, muscle fasciculation, central nervous system depression, convulsions, cyanosis, and coma.[12] Diagnosis is made by history taking or the presence of toxidromes such as acute cholinergic syndrome. The determination of cholinesterase activity is useful in diagnosing acute poisoning in cholinergic intoxication. Cholinesterase depression is usually apparent within a few minutes or hours after significant absorption. A decrease of 25–50% of the individual's baseline enzyme level is usually regarded as evidence of poisoning.[13]

Treatment of cholinergic crisis should provide supportive and symptomatic care. Atropine is often used to reverse muscarinic manifestations that are present in acetylcholinesterase-inhibitor-mediated toxidromes.[13] Pralidoxime administration is also helpful in increasing the plasma cholinesterase activity after rivastigmine poisoning.[14]

Conclusion

Acute cholinergic syndrome due to rivastigmine poisoning is rarely observed in the ED. EPs should be aware of the signs and symptoms of acute cholinergic syndrome and the presence of its toxidromes. As seen in our case, the patient has a good chance of recovery if aggressively managed.

Conflicts of Interest Statement

The authors declare no conflict of interests.

Authors' Contributions

Contribution: Nai-Hui Lin wrote the draft and Yu-Jang Su revised and corresponded. Hsiu-Wu Yang and Hsin-Tang Chen discussed together with Nai-Hui Lin and Yu-Jang Su.

Funding

This study has not received any external funding.

References

1. Müller T. Rivastigmine in the treatment of patients with Alzheimer's disease. *Neuropsychiatr Dis Treat* 2007;3:211-218. doi:10.2147/nedt.2007.3.2.211
2. Lövborg H, Jönsson AK, Hägg S. A fatal outcome after unintentional overdosing of rivastigmine patches. *Curr Drug Saf* 2012;7:30-32. doi:10.2174/157488612800492717
3. Khoury R, Rajamanickam J, Grossberg GT. An update on the safety of current therapies for Alzheimer's disease: focus on rivastigmine. *Ther Adv Drug Saf* 2018;9:171-178. doi:10.1177/2042098617750555
4. Ferreira A, Maroco E, Yonamine, M. Oliveira M. Organophosphate and carbamate poisonings in the northwest of Paraná state, Brazil from 1994 to 2005: clinical and epidemiological aspects. *Revista Brasileira de Ciências Farmacêuticas* 2008;44:407-415. doi:10.1590/S1516-93322008000300010
5. Polinsky RJ. Clinical pharmacology of rivastigmine: a new-generation acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. *Clin Ther* 1998;20:634-647. doi:10.1016/S0149-2918(98)80127-6
6. Kennedy JS, Polinsky RJ, Johnson B, et al. Preferential cerebrospinal fluid acetylcholinesterase inhibition by rivastigmine in humans. *J Clin Psychopharmacol* 1999;19:513-521. doi:10.1097/00004714-199912000-00005
7. Brvar M, Možina M, Bunc M. Poisoning with rivastigmine. *Clin Toxicol (Phila)* 2005;43:891-892. doi:10.1080/15563650500357677
8. Sener S, Ozsarac M. Case of the month: rivastigmine (Exelon®) toxicity with evidence of respiratory depression. *Emerg Med J* 2006;23:82-85. doi:10.1136/emj.2004.017301
9. Hoffman RS, Manini AF, Russell-Haders AL, Felberbaum M, Mercurio-Zappala M. Use of pralidoxime without atropine in rivastigmine (carbamate) toxicity. *Hum Exp Toxicol* 2009;28:599-602. doi:10.1177/0960327109107044
10. Lee DH, Choi YH, Cho KH, Yun SY, Lee HM. A case of rivastigmine toxicity caused by transdermal patch. *Am J Emerg Med* 2011;29:695.e1-695.e2. doi:10.1016/j.ajem.2010.05.024
11. Suzuki Y, Kamijo Y, Yoshizawa T, Fujita Y, Usui K, Kishino T. Acute cholinergic syndrome in a patient with mild Alzheimer's type dementia who had applied a large number of rivastigmine transdermal patches on her body. *Clin Toxicol (Phila)* 2017;55:1008-1010. doi:10.1080/15563650

.2017.1329536
12. Ecobichon DJ. Toxic effects of pesticides. In: Klaassen CD, ed. *Casarett and Doull's Toxicology: The Basic Science of Poisons*. 6th ed. New York, NY: McGraw-Hill; 2001:763-810.
13. Institute of Medicine (US) Committee on Curriculum Development in Environmental Medicine. Case studies in environmental medicine. In: Pope A, Rall D, eds. *Environmental Medicine: Integrating a Missing Element into Medical Education*. Washington (DC), US: National Academy Press;1995:575.
14. Saz EU, Yurtseven A, Kilinç MA, Sari F, Ağin H. The first use of pralidoxime in a child with rivastigmine poisoning. *Pediatr Emerg Care* 2018;34:e184-e186. doi:10.1097/PEC.0000000000001086