

# Case of the month: Rivastigmine (Exelon®) toxicity with evidence of respiratory depression

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Rivastigmine, which has been approved by the US Food and Drugs Administration for the treatment of Alzheimer's disease, is a non-competitive reversible inhibitor of acetylcholinesterase. We present a case of rivastigmine toxicity at a dose of 90 mg, with evidence of respiratory depression. To our knowledge, this case report provides evidence of the highest rivastigmine ingestion recorded (90 mg) that caused respiratory depression but requiring only supportive intervention without the need for raldoxime. Emergency physicians should strongly consider cholinesterase inhibitor (rivastigmine, galantamine, and tacrine) ingestion in patients who present with short and temporary organophosphate-like toxidromes.

Alzheimer's disease (AD) accounts for nearly 70% of dementias and is estimated to affect millions worldwide.<sup>1</sup> It manifests as gradual and progressive decline in cognitive function and ability to perform activities of daily living, and the development of behavioural disturbances.<sup>2</sup> Acetylcholinesterase inhibitors used in the treatment of AD include tacrine, donepezil, galantamine, and rivastigmine, which have been approved by the US Food and Drugs Administration.<sup>3</sup> Like donepezil and tacrine, rivastigmine is a noncompetitive reversible inhibitor of acetylcholinesterase.<sup>4,5</sup> This report illustrates rivastigmine toxicity at a dose of 90 mg, with evidence of respiratory depression.

## CASE REPORT

A 38 year old, 72 kg white man presented to our university hospital emergency department (ED) at 0810, complaining of dizziness, nausea, vomiting, sweating, and salivation approximately 2 hours after ingesting 15 of his grandfather's capsules. Relatives of the patient informed the emergency physician (EP) that they had found an empty package at home that had contained Exelon capsules 6 mg. The patient denied taking any other drug or alcohol and had no other symptoms. He had vomited once approximately 90 minutes after he had taken the drugs but was not sure whether this had expelled any of the capsules. After vomiting, he had developed sweating, salivation, fever, and malaise, and his nephew took him to the ED.

The patient was taking no prior medications and there was nothing notable in his medical or family history. His vital signs were: blood pressure 169/119 mmHg, pulse rate 88 beats/min, respiratory rate 16 breaths/min, temperature 37.7°C, oxygen saturation 97%. He was sleepy but oriented and cooperative, and had a Glasgow Coma Score of 13 (E3M6V4). The skin was damp and warm. There was no fasciculation, and the remainder of the examination was unremarkable.

Bedside blood glucose level was 812 mmol/l. ECG showed no evidence of ischaemia or conduction defects, except bradycardia for a short period when respiratory depression existed. Arterial blood gases, complete blood count,

electrolytes, liver and renal function tests, and cardiac markers were normal. Red blood cell cholinesterase levels were markedly low (table 1).

The patient was admitted to the medical intensive care unit of the ED and placed on a cardiac monitor. An intravenous line was inserted, orogastric catheter placed, and gastric lavage performed. After gastric lavage, 1 g/kg activated charcoal was passed down the orogastric tube. The patient's vital signs changed over time (table 1). A total of 3 mg atropine sulfate was given by means of slow intravenous push to control hypersecretion and bradycardia. After intravenous therapy of 20 mg metoclopramide and 8 mg ondansetron, the nausea and vomiting was brought under control. Supplemental oxygen was given at 4 l/min via nasal cannula. Despite low respiratory rate (~9–10 breaths/min) and oxygen saturation (~91–93%) lasting no more than 30 minutes, there was no need to secure the airway (table 1). Sixteen hours after ingestion, the patient had no symptoms and normal vital signs. A psychiatry consultation was obtained, and the patient was discharged with the diagnosis of rivastigmine toxicity and impulsive suicide attempt.

## DISCUSSION

Rivastigmine, which exerts its effect by increasing the availability of intrasynaptic acetylcholine, has been demonstrated to be effective in the treatment of the cognitive deficits of AD.<sup>6–9</sup> Unlike organophosphates, which bind irreversibly, and carbamates, which bind reversibly for 8–10 hours, rivastigmine binds 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 (~4–6 hours) induced by rivastigmine is longer than its half-life (~1 hour).<sup>10,11</sup> Although none of the diagnostic studies, except a reliable history, is adequate to distinguish acetylcholine excess toxidromes, ideally organophosphate toxicity diagnosis is based on a 50% decrease in red blood cell cholinesterase from pre-exposure baseline activity (only occupational workers frequently exposed to organophosphates have their baseline levels on file).<sup>12</sup>

In the literature, only one case of rivastigmine overdose has been reported, with 46 mg rivastigmine tartrate; the patient experienced vomiting, incontinence, hypertension, psychomotor retardation, and loss of consciousness.<sup>13</sup>

EPs should be aware of the signs of increased nicotinic (fasciculation, hypertension, muscle weakness), muscarinic (nausea, vomiting, diarrhoea, urination, mydriasis, sweating, bronchorrhoea, salivation, and reduction of sinus node and AV conduction, causing bradyarrhythmias, hypotension, or resultant ventricular dysrhythmias) and especially central nervous system effects (seizure), which are the same as with organophosphate and carbamate toxicities, but last longer. Treatment should be symptomatic, using atropine to reverse

**Abbreviations:** AD, Alzheimer's disease; ED, emergency department; EP, emergency physician

**Table 1** Post-presentation vital signs and (RBC) chE levels measured over time

	Time after admission (hours)				
	0	2	6	12	16
BP (mmHg)	169/119	118/72	138/92	124/83	123/76
RR (/min)	16	10	18	16	16
HR (/min)	88	50	94	86	75
SpO <sub>2</sub> (%)	97	91	97	99	98
(RBC) chE	947	1013	1507	1980	2901

BP, blood pressure; RR, respiratory rate; SpO<sub>2</sub>, oxygen saturation; HR, heart rate; (RBC) chE, red blood cell cholinesterase (measured in U/g haemoglobin; normal range 2710–11510).

muscarinic manifestations and benzodiazepines to stop seizures, and supportive, as with all of the acetylcholinesterase inhibition mediated toxidromes. Pralidoxime should be reserved for patients with or at risk for skeletal muscle weaknesses, such as respiratory insufficiency, in cases where there is no reliable history and the EP must rely on the diagnosis. Because of the short half-life of rivastigmine, dialysis would not be clinically indicated.

To our knowledge, this case report provides evidence of the highest rivastigmine ingestion recorded (90 mg) that caused respiratory depression but requiring only supportive interventions without the need for pralidoxime (2-PAM). EPs should strongly consider cholinesterase inhibitor (rivastigmine, galantamine, and tacrine) ingestion in patients who present with short and temporary organophosphate-like toxidromes.

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