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Selected Topics: Toxicology

TRANSIENT CARDIAC EFFECTS IN A CHILD WITH ACUTE CHOLINERGIC SYNDROME DUE TO RIVASTIGMINE POISONING

Umberto Raucci, MD, PHD,* Nicola Vanacore, MD, PHD,† Corrado Cecchetti, MD,* Mario Salvatore Russo, MD,‡ Rossella Rossi, MD,* and Nicola Pirozzi, MD*

*Pediatric Emergency Department, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, †National Centre for Epidemiology, Surveillance, and Health Promotion, National Institute of Health, Rome, Italy, and ‡Paediatric Arrhythmology Unit and Syncope Unit, Paediatric Cardiology and Heart-Surgery, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

Reprint Address: Umberto Raucci, MD, PHD, Pediatric Emergency Department, Bambino Gesù Children's Hospital, IRCCS, Sant. Onofrio Place 4, Rome 00165, Italy

☐ **Abstract—Background: We report a case of rivastigmine poisoning resulting in a full cholinergic syndrome with nicotinic, muscarinic, and central effects requiring supportive or intensive care in a pediatric patient. Case Report: A 3-year-old girl was admitted to the Emergency Department suspected of having ingested one or two pills of rivastigmine. The child was hyporeactive, with symptoms of altered mental status, sialorrhea, sweating, and diarrhea. Subsequently, she started showing signs of respiratory failure, severe tracheobronchial involvement, and gastric and abdominal distension. An electrocardiogram recorded frequent monomorphic ventricular ectopic beats with bigeminy and trigeminy. Long-term follow-up showed a transient dysrhythmia. Conclusion: Poisoning with rivastigmine can be a life-threatening condition. Timely identification and appropriate management of the toxic effects of this drug are essential and often life-saving. This is particularly true in cases of cholinergic syndrome subsequent to drug poisoning. Patients with cholinergic syndrome should also be assessed for possible cardiac complications such as dysrhythmias. The main factors predisposing to the development of such complications are autonomic disorder, hypoxemia, acidosis, and electrolyte imbalance.** © **2014 Elsevier Inc.**

☐ **Keywords—rivastigmine; cholinergic syndrome; toxicity; poisoning; cardiac effect**

INTRODUCTION

Rivastigmine is one of the three cholinesterase inhibitors, the others being donepezil and galantamine, currently indicated for the treatment of cognitive symptoms in probable Alzheimer's disease (1). Estimated cases of dementia are currently over 35.6 million, though this number is expected to increase, doubling every 20 years, so as to reach 115.4 million people in 2050 (2). It is estimated that 1 in 10 patients with dementia in Europe is treated with cholinesterase inhibitors (3).

Rivastigmine is a noncompetitive, reversible, acetylcholinesterase inhibitor (1). Some cases of poisoning or toxicity due to overdose with rivastigmine are described in adults (4–7). To our knowledge, only one case of poisoning with rivastigmine has been reported in a child: an 11-month-old girl who accidentally chewed a rivastigmine capsule and showed only nicotinic effects (hypotonia, hyporeflexia, miosis, and weak cry) (8).

We report the second pediatric case of poisoning subsequent to the accidental ingestion of rivastigmine. Our patient is the first reported case with full cholinergic syndrome (ChoS), including respiratory failure and transient cardiac complications, which resulted in a favorable outcome.

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CASE REPORT

A 3-year-old, otherwise healthy, Italian girl was admitted to the local Emergency Department (ED) 45 min after a suspected ingestion of rivastigmine. The child was conceived by healthy, nonconsanguineous parents and delivered uneventfully by natural childbirth. She was not taking any medication prior to admission, and had normal psychomotor development. Rivastigmine had been prescribed to her paternal grandfather for the treatment of Alzheimer's disease. The child ingested one or two of these colored pills, each containing 4.5 mg of rivastigmine, which had been left on the table at home. Upon arrival at the ED the child was in good general condition, alert and oriented, but restless. During the following few minutes, the child started showing signs of altered mental status, confusion and drowsiness, hyporeactivity to environmental stimuli, sialorrhea, sweating, and had two episodes of diarrhea. She was diagnosed with possible rivastigmine-related Chos. Subsequently, the child started showing signs of respiratory failure, tachypnea, severe tracheobronchial involvement, and gastric and abdominal distension. She displayed low values of pulse oximetry and oxygen saturation equal to 90%, and electrocardiographic monitoring showed sinus tachycardia reaching 180 beats/min. An enteral tube was positioned and gastric lavage was performed, followed by administration of 1 g/kg of activated charcoal through a nasogastric tube. Subsequent neurological assessment showed progressive deterioration with mental impairment. The child showed psychomotor agitation and miosis, and localizing and lateralizing neurological signs were absent. She was intubated and ventilated by an anesthesiologist who used propofol for sedation and vecuronium bromide for paralysis. She was administered 0.05/mg/kg of atropine sulfate via intravenous infusion, followed by additional 0.02 mg/kg 30 min later. Her condition improved, and she was transferred to our hospital. The child was admitted to the intensive care unit of our ED and placed on multiparametric monitoring. Analgosedation was induced with midazolam and remifentanil, and she was put on volume-controlled mechanical ventilation.

Laboratory tests showed a marked reduction of serum cholinesterase levels, with a value of 732 U/L (normal range 3000−11,000 U/L), hyperglycemia (238 mg/dL), and neutrophil leucocytosis (20,140/μL, 78.2% neutrophils). Electrolytes, liver, and renal function tests were within normal limits. Electrocardiography (ECG) showed sinus rhythm at 134 beats/min, normal atrioventricular conduction, normal QT interval, and frequent ventricular and monomorphic ectopic beats (VEBs) with bigeminy and trigeminy. Echocardiography showed no abnormalities.

Serum cholinesterase levels increased progressively to normal ranges in the subsequent hours (2008 U/L, 3640 U/L, 7452 U/L, 8110 U/L at 5.30, 12, 20, and 36 h, respectively). These values were obtained as per hospital policy. Other blood values and pH levels normalized as well. Thirteen hours after admission to our hospital, the child was weaned from mechanical ventilation and, after reduction of analgosedation, she was extubated. Neurological assessment was normal. VEBs persisted after extubation, with the same characteristics as previously described.

Twenty-four hours after admission, the girl was transferred to our Cardiology Unit to undergo 24-h Holter ECG monitoring. The test recorded 72 episodes of nonsustained ventricular tachycardia (maximum 3 beats), 473 couplet episodes, 1445 bi-trigeminy runs, and 5459 isolated beats out of 121,500 total beats (14.6%). The maximum number of VEBs per hour was 2065. No supraventricular activity was detected. Atrioventricular conduction was normal, and no R-R intervals > 2.0 s were recorded. The patient was discharged from the hospital after 4 days with no cardiac symptoms and no need of further therapy.

The child showed no signs or symptoms suggestive of palpitations at subsequent outpatient visits. Follow-up ECG was within normal ranges, whereas the Holter ECG showed frequent isolated VEBs. The patient was followed-up in an Arrhythmology Unit for the following 8 years. She remained asymptomatic, showed neither palpitations nor syncope, and Holter ECG monitoring at 5 years showed 3016 isolated monomorphic VEBs out of 109,920 total beats (2.7%). The stress test showed a reduction of dysrhythmia, which disappeared at a higher cardiac frequency. The Holter ECG, 6 years later, showed 77 monomorphic and isolated VEBs out of 96,308 total beats. The twice yearly Holter ECG monitoring that followed did not record any dysrhythmia. The patient is currently doing well, figure skating at a competitive level.

DISCUSSION

Rivastigmine is a centrally acting, pseudo-irreversible, selective acetylcholinesterase and butyrylcholinesterase inhibitor used for the treatment of Alzheimer's disease (9). Reports have also been published about its off-label use in children with autism spectrum disorders and Down syndrome (10–12). Our patient is, to our knowledge, the second reported pediatric case of rivastigmine poisoning with a subsequent ChoS similar to the syndrome caused by organophosphate poisoning (Table 1). The first case was reported by Lai et al. and referred to a child who was admitted to the ED showing only nicotinic effects and needing neither supportive