Etizolam overdose in an eight-year-old boy

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CASE

An 8-year-old male presented to the Kelowna General Hospital's emergency department (ED) with severe ataxia, slurred speech, and altered level of consciousness. A thorough history was challenging due to the patient's inability to speak coherently and both parents seeing him as healthy before he went to school. His sister described him as being completely well before their separation and him walking to his classroom. His Glasgow Coma Scale score at that time was 11. He denied ingestion of any substances and had not had any episodes of emesis, fever, rashes, or bites.

Further conversation with his parents revealed a noncontributory family history; medical history was unremarkable, and there had been no history of seizures, developmental delays, or environmental exposures. On examination, his initial vital signs showed a heart rate of 92, respiratory rate of 18, oxygen saturation of 100% on room air, blood pressure of 116/92, temperature of 36.4°C, and he weighed 30 kg. His cranial nerve exam showed bilateral vertical and horizontal nystagmus and a relative afferent pupillary defect of his left eye. He had reduced power of his upper and lower extremities, to minimal movement against gravity. This was believed to be a consequence of his incoordination and not true muscle power loss. There was no hyperreflexia, clonus, or spasticity in his movement. He had loss of truncal tone when repositioned. He was unable to perform any coordination exams, such as nose-finger, rapid alternating movements, or heel-shin assessment. He was unable to stand, so Romberg assessment and gait analysis could not be evaluated. His abdominal, cardiovascular, respiratory, HEENT, and dermatological exams were unremarkable.

Cerebellar dysfunction was suspected, and due to the acute presentation of his symptoms, a toxin ingestion was believed to be the primary diagnosis. Due to his broad differential diagnosis, the patient received a comprehensive work-up for his altered level of consciousness. Toxicology assessment of blood and urine were negative for ethanol, opiates, cocaine, benzodiazepines, methamphetamine, tetrahydrocannabinol, and oxycodone ingestion. CT, CT angiogram, and brain MRI all showed no significant intracranial abnormalities. Lumbar puncture showed no infective processes. An electroencephalograph showed the presence of beta waves, which was interpreted by the neurologist as a common feature of benzodiazepine ingestion.

The MRI was performed under anesthesia approximately 10 hours after his presentation to the ED. He received propofol and dexmedetomidine before this procedure. His symptoms continued to improve, and he was finally able to articulate that he had ingested a pink substance from his classroom. The pediatric team provided intensive observation overnight, as the substance could still not be identified, and the possibility of further sequelae were not yet known. He continued to improve, and roughly 18 hours after his initial presentation, his symptoms had resolved, and the patient was discharged without further complications. He was reassessed 3 weeks later, and there was no recurrence of any symptoms or presence of long-term sequelae. The substance was located by the school principal and brought to the hospital, where it was sent to ProvLab in Vancouver, and was identified as etizolam by mass spectrometry.

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Figure 1 The pink powder that was discovered underneath a desk in the patient's 3rd grade classroom.

DISCUSSION

Etizolam is a relatively rare drug in North America but is routinely prescribed in some Asian countries for the use of generalized anxiety disorder with depressive symptoms.[1] However, the Blue Ridge Poison Center in America called etizolam an emerging drug of concern and describe an upward trend in poison control center calls and Internet searches regarding this drug.[1] It is structurally different but pharmacologically similar to benzodiazepines, both having gamma aminobutyric acid (GABA) type A receptor agonism, which is the primary inhibitory neurotransmitter of the central nervous system. This is clinically relevant because intentional ingestions of benzodiazepines typically involve coingestants, the most common being ethanol, which can lead to substantial respiratory depression and airway compromise.[2] The dose required to produce respiratory compromise is difficult to quantify and depends on dosage, tolerance, weight, age, and coingestants,[2] which is what makes this situation interesting, because the patient presumably ingested etizolam without coingestants and had such significant symptoms.

There have been three case reports of suspected overdose on etizolam. Two resulted in patient fatalities, but these deaths could not be exclusively attributed to etizolam overdose.[3] The last was that of a 17-month-old girl from Japan that had spontaneous resolution of her symptoms approximately 16 hours after known ingestion of etizolam.[4] She experienced paradoxical excitation with muscle weakness and agitated speech. All these cases together indicate that very little is known about the sequelae of ingestion of this drug, and even less on the consequences in children.

The British Columbia toxicology screen is extremely reliable in identifying a spectrum of toxins, but current techniques are unable to detect etizolam in blood or urine. Immunoassays for urine drug screening only detect benzodiazepines metabolized to oxazepam glucuronide; etizolam is metabolized to α-hydroxyetizolam,[1] which is currently undetectable without mass spectrometry, requiring its shipment to a tertiary site that has this resource.[5] Due to this undetectability, our patient required a thorough work up to ensure harmful disease pathologies, such as intracranial catastrophe, stroke, tumor, infection, or seizures, were not causing his symptoms, even though toxin ingestion remained the most likely diagnosis. Benzodiazepine overdose can be successfully reversed by the $GABA_A$-receptor antagonist flumazenil,[1] which could have been provided had we been more confident that an ingestion had occurred.

A biological sample confirming the presence of etizolam in this child was never obtained. His blood and urine samples did not confirm the presence of this drug in his system, and the strongest indicator of its ingestion was the electroencephalograph findings by the neurologist, along with the patient's clinical presentation, which is common in benzodiazepine overdose. Therefore, only a strong opinion can be had that the substance that was found in the patient's classroom, which was confirmed to be etizolam, was in fact the substance that he had ingested. The goal of this case is to highlight to clinicians that more awareness is necessary on the possibility of etizolam ingestion, especially in a nonverbal patient, while appreciating that current toxicology screening is not yet able to detect this drug in a patients' system, so having a high index of suspicion is critical in ensuring the correct diagnosis.

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