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Case Report

Atypical Antipsychotic Toxidrome: A Case Report and a Proposed New Toxicity Syndrome

Hanna S. Sahhar*, Maichoua S. Lor, Lauren Bailey

Department of Pediatric, Edward Via College of Osteopathic Medicine (VCOM)-Carolinas, Spartanburg, South Carolina 29303, United States

ABSTRACT

Quetiapine is an atypical antipsychotic medication approved by the U.S. Food and Drug Administration to treat psychosis and mood disorders. Side effects of quetiapine when used at therapeutic levels include sedation, weight gain, and orthostatic hypotension. Quetiapine toxicity in overdose or misuse presents with autonomic instability, miosis, hypotension, extrapyramidal symptoms, and QTc interval prolongation. We present a unique case of an unsuspected quetiapine overdose in a 17-year-old male with comorbid untreated epilepsy. The patient presented with acute dystonia, central nervous system depression, and miosis. The patient required endotracheal intubation and mechanical ventilation and was treated with supportive care. He subsequently developed neuroleptic malignant syndrome and aspiration pneumonia. The patient recovered completely without residual symptoms. We propose that atypical antipsychotic toxicity should be recognized as a toxidrome category for pediatric and adolescent patients.

Keywords: Quetiapine; Overdose; Toxicity; Toxidrome; Atypical antipsychotics; Adolescent

INTRODUCTION

Antipsychotics are a class of medication primarily indicated to treat psychiatric disorders such as schizophrenia, bipolar disorder, and treatment of refractory behavioral disorders. Antipsychotics can be divided into typical antipsychotics, or first-generation, and the newer atypical antipsychotics, or second and third generations. In this case, we focus on Atypical Antipsychotics (AAPs) which have grown in favor due to a more desirable side effect profile [1]. Aripiprazole, Asenapine, Clozapine, Iloperidone, Lurasidone, Olanzapine, Paliperidone, Quetiapine, Risperidone, and Ziprasidone are approved by the Food and Drug Administration (FDA) to treat varying behavioral and mental health disorders in children and adolescents. However, many physicians are using AAPs off-label to treat behavioral issues in children, making them even more accessible in this population [2].

Quetiapine is commonly used to treat bipolar and schizophrenia in adolescents [3]. Historically, quetiapine overdoses occurred in patients with mental health diagnoses that were prescribed this medication for treatment. However, like other pharmaceuticals, adolescents may abuse quetiapine without a prescription. Multiple studies suggest that quetiapine is the most likely AAP to be abused [4], making this toxidrome especially important for healthcare providers to recognize. Due to its action on multiple neurotransmitter receptors, it has a wide variety of possible side effects. Quetiapine acts as a serotonergic 5-hydroxytryptamine antagonist, D1 and D2 dopaminergic antagonist, H1 histaminergic antagonist, and alpha-1 and alpha-2 adrenergic antagonist [3]. When used at therapeutic levels, quetiapine can cause side effects of weight gain, sedation, and orthostatic hypertension [2].

CASE PRESENTATION

A 17-year-old Caucasian male with a known medical history of seizures, Major Depression Disorder (MDD), Generalized Anxiety Disorder (GAD), insomnia, Attention Deficit Hyperactivity Disorder (ADHD), and asthma presented to the Emergency Department (ED) *via* Emergency Medical Services (EMS) for evaluation of altered mental status. The patient was discovered unresponsive and exhibiting seizure activities on his bedroom floor by his mother at 9 am that morning. The mother

Correspondence to: Hanna S. Sahhar, Department of Pediatric, Edward *Via* College of Osteopathic Medicine (VCOM)-Carolinas, Spartanburg, South Carolina 29303, United States, E-mail: hsahhar@vcom.edu

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noted there was vomitus around his mouth [4]. The patient was last seen by his family at 11 pm the previous night in a normal condition. The patient was reported to be with his friends before discovery in his room. The patient's friends reported that he smoked marijuana and may have invested approximately 8-10 pills of 4-year-old expired valproate and unknown amount of alprazolam.

Vital signs taken by EMS during transport included a blood pressure of 137/68 mmHg, heart rate of 150 beats/minute, respiratory rate of 8 breaths/minute with shallow effort, and oxygen saturation of 80% on room air. Oxygen saturation increased to 90% with the support of 15 L/minute non-rebreather mask. EMS noted that the patient moaned to painful stimuli and was rigid with intermittent posturing activity. Glasgow Coma Scale (GCS) Score was [6]. Naloxone 2 mg dose was administered intranasally due to a suspected drug overdose with no response.

Upon arrival to the ED at 9:54 am, physical examination revealed an unconscious, unresponsive teenager with pinpoint pupils and decerebrate posturing. GCS estimated to be 4. He was drooling with agonal breathing and had diminished air entry to the right upper lobe on auscultation. Vital signs showed the patient was afebrile but tachycardic at 144 beats/minute. Blood pressure increased to 164/110 mmHg. The patient was tachypneic at 33 breaths/minute with oxygen saturation at 100% on the non-rebreather mask. The patient was immediately endotracheally intubated for airway protection and received a 20 ml/kg normal saline fluid bolus. A loading dose of 20 mg/kg of levetiracetam was given intravenously (IV), in addition to 3 doses of lorazepam of 0.1 mg/kg IV each dose and 2 doses of propofol of 1 mg/kg IV each dose in an attempt to mitigate decerebrate posturing without resolution. One dose of 50 g of activated charcoal was given through nasogastric tube due to unclear timeline and unknown ingestants. Laboratory investigations revealed an elevated plasma lactic acid level at 3.1 mmol/L (NR 0.3–2.1 mmol/L), elevated C-reactive protein (CRP) of 1.10 mg/dL (NR 0.00–0.60 mg/dL), and normal creatine kinase of 71 IU/L (NR 30–223 IU/L). Complete blood count (CBC) and comprehensive metabolic panel (CMP) were unremarkable except for a high blood glucose level of 216 mg/dL (NR 60–100 mg/dL). Valproic acid blood level was below therapeutic threshold at 43.0 ug/mL (therapeutic level 50–100 ug/mL). Salicylate, acetaminophen, and ethanol blood levels were negative. Urine drug screen was positive for marijuana and negative for amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, oxycodone, and phencyclidine.

Computed Tomography (CT) scan of the head was negative for acute intracranial abnormalities. Chest radiography revealed a hazy opacity along the right side of the mediastinum in the suprahilar and hilar regions. Electrocardiogram (ECG) showed a normal corrected QT interval (QTc) of 339 msec (normal ≤ 460 msec for age). The patient was admitted to the pediatric intensive care unit (PICU) for further evaluation and management.

In the PICU, the patient's blood pressure improved to 118/85 mmHg while his heart rate remained high at 141 beats/minute. A repeat ECG revealed moderately extended QTc interval at 441 msec. Consultation with neurologist was initiated and the patient subsequently underwent an electroencephalogram (EEG) to evaluate for epileptiform activity. The EEG showed background rhythms of low voltage poorly organized frontal 2-4 Hz delta activity with superimposed moderately high amplitude 15 Hz beta activity continuously. There were no focal slowing or epileptiform activities noted. These abnormal EEG results were consistent with a diffuse encephalopathy likely secondary to sedation by medication used for intubation and/or overdose. The patient was started on valproic acid at a dose of 10 mg/kg IV every 8 hours due to his history of untreated seizures.

Later that afternoon, the patient exhibited an elevated temperature of 40.7°C (105.2°F) and was hypotensive at 86/44 mmHg with heart rate of 170 beats/minute. Antipyretic in the form of acetaminophen at a dose of 15 mg/kg rectally was given with no response. The patient was started on acyclovir of 10 mg/kg IV every 8 hours for suspicion of potential meningitis infection. Around 12 hours after arrival to the ED, the patient's mother told the primary healthcare team that the patient may have ingested quetiapine.

On day two of his hospital stay, repeat chest radiography confirmed the diagnosis of aspiration pneumonia in the right upper lobe. The patient was started on clindamycin of 10 mg/kg IV every 6 hours. His temperature improved to normal limits. An ECG exhibited continued borderline QTc prolongation of 446 msec. Brain magnetic resonance imaging (MRI) showed no evidence of acute abnormalities. Brain magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) both showed patent vessels with no occlusion or stenosis. A lumbar puncture was also performed to rule out meningitis. Cerebrospinal fluid studies were all negative, subsequently, acyclovir was discontinued.

RESULTS

On day three, the patient's CRP increased to 16.80 mg/dL. His respiratory culture returned positive for methicillin-resistant staphylococcus aureus (MRSA). Intravenous clindamycin was continued for appropriate coverage of MRSA. The psychiatrist recommended follow up with outpatient mental health and was restarted on fluoxetine 10 mg orally once daily for anxiety and depression. The patient was discharged home on the fourth day of his hospital stay to continue oral valproic acid of 500 mg every 8 hours and oral clindamycin of 600 mg every 8 hours for seven days, in addition to the fluoxetine (Table 1).

DISCUSSION

We describe a case of quetiapine overdose in an adolescent male presenting with CNS depression, initial hypertension, hyperglycemia, seizures, and miosis. Historically, quetiapine overdose occurred in patients with prior diagnosis of schizophrenia or mood disorder with prescribed quetiapine. In recent years, AAP abuse has led to increasing numbers of AAPoverdoses. Our patient was not prescribed quetiapine, making it the less obvious choice for diagnosis at initial presentation. We propose that atypical antipsychotic toxicity should be recognized as a new toxidrome category for pediatric

Table 1: The proposed new atypical antipsychotic toxidrome, selected drugs, presentation of toxicity, and treatment options.

Toxidrome	Agents/Drugs	Presentation				Treatment/ Antidote
		Vital signs	Skin	Pupils	Neuro/Mental status	
Atypical Antipsychotic	Aripiprazole Asenapine Clozapine Iloperidone Lurasidone Olanzapine Paliperidone Quetiapine Risperidone Ziprasidone	Hypotension Tachycardia Hyperthermia	Normal	Miosis or Variable	Sedation Seizures Coma Variable Extrapyramidal Symptoms (EPS)	Supportive care Benzodiazepines Benztropine Diphenhydramine

patients.Unfortunately, we did not have a high clinical suspicion for quetiapine as the drug of overdose early in the clinical presentation. We considered other possible etiologies of his initial presentation including valproate and alprazolam overdose per the mother's initial statement. Valproate is used to treat seizure disorders, mood disorders, and neuropathic pain [6]. These patients are usually normotensive. Respiratory depression is less likely to be seen in alprazolam overdose without coingestion but has been reported in 10% of pediatric cases [7]. In this case, the patient's urine drug screen was negative for benzodiazepines. It should be noted that AAP overdoses may also present similarly to opioid and alpha 2-adrenergic agonist overdoses [2]. In our case, the patient did not respond to intranasal naloxone administration. There was also no history to suggest opioid use. Aside from cannabinoids in the urine, we have no reason to assume that drug interactions or polypharmacy were involved in this overdose. We objectively conclude that this is a case of quetiapine overdose, which aligns with clinical findings and family statements.

It should be considered that the episode of elevated temperature, hypotension, and tachycardia was likely Neuroleptic Malignant Syndrome (NMS). NMS is characterized by its tetrad of altered mental status, muscular rigidity, hyperthermia, and autonomic instability [2]. Because of its variable clinical manifestations, NMS is underdiagnosed and underreported [2]. Our patient had an atypical presentation of NMS without muscle rigidity, similar to another case reported by Teo et al. [5]. Teo reported a case of a 43-year-old man who overdosed on clozapine and quetiapine and had a delay in diagnosis due to the lack of muscle rigidity.

If we had a higher suspicion for quetiapine overdose, we would have ordered a quetiapine blood level on admission. Additionally, we would have ordered a CBC to check for elevated white blood cell count following the NMS diagnosis. Our patient's overdose was successfully treated with supportive care including endotracheal intubation and mechanical ventilation, anti-epileptic medications, and intravenous fluids. The patient made a full recovery after completion of antibiotics for aspiration pneumonia due to MRSA.

CONCLUSION

AAP toxicity should be included in the toxicologic differential diagnosis of a patient with a similar presentation of CNS depression, tachycardia and miosis with unknown history of pharmacologic drug use table. We propose that atypical antipsychotic toxicity should be recognized as a new toxidrome category for pediatric and adolescent patients. Due to increased incidence of AAP overdose, recognizing this toxidrome will be useful for healthcare providers who may care for patients with similar presentations. Patients may display variable neurophysical symptoms, especially in the context of complex comorbidities which may make diagnosis more difficult. In this case, an adolescent male with untreated epilepsy presented after quetiapine overdose with seizures, CNS depression, dystonia, tachycardia and miosis. The patient subsequently developed NMS and MRSA aspiration pneumonia.

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