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Occult Valproic Acid Toxicity Unmasked After Physostigmine Administration

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Case Report

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Abstract: Psychotropic medication overdoses are common, but patients are frequently unwilling or unable to identify their ingestant(s). We describe a case of a woman who developed antimuscarinic toxicity after ingesting quetiapine. Once her delirium was successfully treated with physostigmine, she was able to report co-ingesting valproic acid, for which she required hospital admission and antidotal therapy with L-carnitine. We recommend that, unless contraindicated, physostigmine should be administered in cases of moderate-to-severe antimuscarinic poisoning, both to treat the delirium and peripheral manifestations and as a diagnostic aid to obtain a more complete history.
Keywords: quetiapine; valproic acid; physostigmine; antimuscarinic

INTRODUCTION

Drug overdoses are commonly encountered in the emergency department (ED), but patients are frequently unable or unwilling to identify the ingestant(s). Treating physicians must use a combination of historical features, physical exam findings, and laboratory results to narrow the differential diagnosis, but often a precise diagnosis is impossible. Serum drug measurements are available in a clinically-meaningful timeframe for only a small percentage of xenobiotics, and urine drug testing, which is often limited to common substances of abuse, is complicated by a high incidence of false-positive and false-negative results.

Antidotes that can reverse central nervous system (CNS) and respiratory depression are often used to prevent the need for endotracheal intubation and mechanical ventilation. They may also facilitate better history-taking. Naloxone use, for example, was reported to regional poison centers 21,933 times in 2015, and many more cases undoubtedly went unreported [1]. Other antidotes, such as flumazenil and physostigmine, are used much less frequently.

We recently treated a patient who presented to the ED with altered mental status and tachycardia following a quetiapine overdose. History was limited by her antimuscarinic delirium. Once she was treated with physostigmine, however, it was possible to obtain additional history that led to a significant change in her management.

CASE REPORT

A 27 y/o female with a history of psychosis presented to the ED five hours after intentionally ingesting an unknown amount of quetiapine, which was her only prescription medication, along with a small volume of liquid cough medicine and vodka. She was noted to be confused and unable to provide a complete history or review of systems. Her vital signs were: heart rate 118 beats/minute, blood pressure 109/63 mm Hg, respiratory rate 18 breaths/ minute, temperature 98.3°F (36.8° C) and oxygen saturation 100% on room air. Her examination was notable for diminished bowel sounds, moderate urinary bladder distention, and pupils that were 8 mm and minimally reactive. Cardiopulmonary examination was remarkable for tachycardia only. Her neurological examination revealed no motor or sensory deficits, no clonus, no rigidity, no hyperreflexia, no tremor, and no nystagmus. She was unable to answer most questions, and when she did speak her speech was noted to be mumbled. She frequently stopped speaking mid-sentence.

Common diagnostic studies, including electrocardiogram (EKG) and laboratory tests, were obtained. The EKG revealed sinus tachycardia with normal intervals and normal axis. There was no evidence of ischemia or injury. Laboratory tests were notable for a mildly elevated ethanol level and a mildly elevated acetaminophen level that did not warrant antidotal therapy with N-acetylcysteine (table 1).

The patient became increasingly delirious and tachycardic, and medical toxicology was consulted over the phone. Toxicology recommended treating the patient with physostigmine, but the primary team was not familiar with the antidote and did not feel

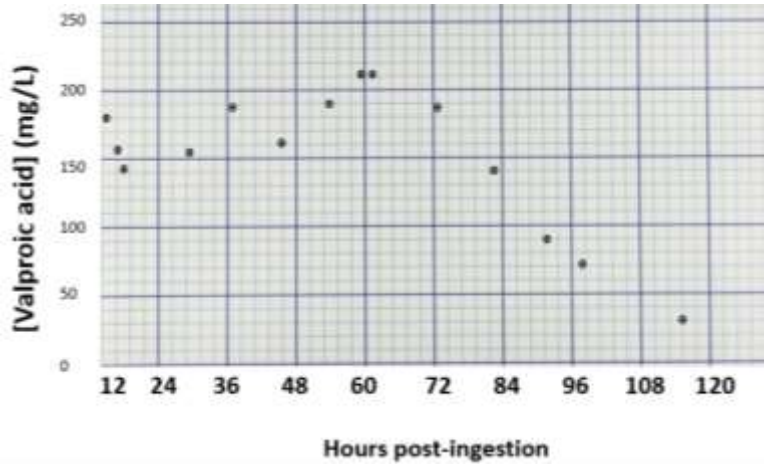
comfortable using it. She was instead treated with a 2-liter intravenous bolus of normal saline and two doses of intravenous lorazepam, each 1 mg. At change of shift two hours later, the patient was still tachycardic and delirious. The oncoming physician re-consulted medical toxicology, and the patient was treated with 2 mg of physostigmine. Within five minutes, the patient was awake, alert, oriented, and cooperative. Her tachycardia also resolved.

The patient was able to provide a complete history afterward, and she acknowledged ingesting between 25 – 35 of her own 100 mg quetiapine tablets as well as several ounces of vodka. She estimated that she drank between 20 – 40 milliliters of a cough and cold product that contained acetaminophen, diphenhydramine, and guaifenesin. She also admitted to ingesting approximately 40 valproic acid (VPA) tablets she had recently stolen from a friend. A VPA level was sent and returned elevated at 167 mg/L (therapeutic range 50 – 100 mg/L). An ammonia level was also sent and returned elevated at 49 μmol/L (reference range 11 – 32 μmol/L).

The patient was started on intravenous L-carnitine and admitted to the hospital. Serial VPA levels were obtained over the ensuing five days (figure 1). L-carnitine was re-dosed every six hours until the VPA level was below 100 mg/L. The patient did not develop any additional signs or symptoms while in the hospital, and she was discharged to a psychiatric facility.

Table-1: Initial Laboratory Test Results

	Patient's results	Reference range
Sodium	136 mmol/L	(136 – 145 mmol/L)
Potassium	3.5 mmol/L	(3.8 – 5.2 mmol/L)
Chloride	100 mmol/L	(98 – 107 mmol/L)
Bicarbonate	21 mmol/L	(21 – 32 mmol/L)
Blood urea nitrogen	4 mg/dL	(7 – 28 mg/dL)
Creatinine	1 mg/dL	(0.6 – 1.3 mg/dL)
Glucose	96 mg/dL	(74 – 106 mg/dL)
Calcium (ionized)	1.19 mmol/L	(1.15 – 1.29 mmol/L)
AST	4 U/L	(15 – 37 U/L)
ALT	12 U/L	(12 – 78 U/L)
Acetaminophen	11.3 mg/L	(10 – 30 mg/L)
Salicylate	undetectable	(2.8 – 20 mg/dL)
Ethanol	35 mg/dL	(negative)
Pregnancy test	negative	(negative)
Urine drug screen: amphetamines	negative	(negative)
Urine drug screen: barbiturates	negative	(negative)
Urine drug screen: benzodiazepines	negative	(negative)
Urine drug screen: cocaine	negative	(negative)
Urine drug screen: opioids	negative	(negative)
Urine drug screen: phencyclidine	negative	(negative)
Urine drug screen: cannabinoid	negative	(negative)



Fig−1: Valproic acid concentration following overdose

DISCUSSION

Quetiapine is a commonly-prescribed atypical antipsychotic of the benzepine class. Patients who are prescribed neuroleptics have a high incidence of suicide attempts, and quetiapine contributed to 22 deaths in 2015[1]. Acute toxicity following overdose manifests as a combination of altered mental status, tachycardia, occasional electrocardiographic manifestations, and central and peripheral antimuscarinic effects[2,3].

Most cases of antimuscarinic toxicity in general, and quetiapine poisoning in particular, are treated supportively. However, there is an antidote that can immediately reverse delirium as well as most of the peripheral manifestations of antimuscarinic poisoning, and its use has been very successful in treating quetiapine toxicity[4].

Physostigmine is a cholinesterase inhibitor derived from the calabar bean, *Physostigma venenosum*. By inhibiting cholinesterase, it allows acetylcholine to accumulate in the synapse and compete with various muscarinic cholinergic receptor antagonists. Because physostigmine is a non-polar tertiary amine, it can cross the blood-brain barrier and reverse central toxicity, which can range from CNS depression to delirium. Recommended dosing in adults is 0.5 – 2 mg, and the dose can be repeated every 30 minutes as needed. The pediatric dose is 0.02 mg/kg. In 1970 its use was reported to reverse antimuscarinic toxicity in a toddler who ingested amitriptyline, but by the 1980s its popularity waned following reports of cardiotoxicity, including asystole [5, 6].

Authors have since speculated that the adverse events that followed physostigmine administration were due to the severe poisonings rather than the antidotal therapy. They have concluded that physostigmine actually reverses cardiotoxicity from tricyclic antidepressants and other sodium channel poisoners, and that TCA ingestion is not a contraindication to its use [7] Contraindications to the use of physostigmine include (1) allergy to any component of the drug, including salicylates, (2) severe asthma, (3) bradycardia or heart block, (4) mechanical obstruction of the genitourinary or gastrointestinal tracts.

The incidence of adverse events following physostigmine use is low. A retrospective study of 39 adult patients treated with physostigmine found that the antidote was 100% successful in treating antimuscarinic toxicity and there were no cases of cardiotoxicity or cholinergic excess [8]. Although one patient did have a seizure after receiving physostigmine, the same patient had had a seizure prior to being treated.

Another retrospective study suggested that physostigmine is safer and more effective than benzodiazepines in the setting of antimuscarinic toxicity [9]. In 52 patients with poisoning from a variety of xenobiotics; physostigmine controlled the agitation and reversed the delirium in 96% and 87% of patients, respectively. Benzodiazepines controlled agitation in 24% of patients and did not reverse any delirium. Additionally, patients who were initially treated with physostigmine had a 7% incidence of complications compared to 46% of patients who were first treated with benzodiazepines. Finally, patients who were treated with physostigmine had a faster recovery time than patients who received benzodiazepines.

A common argument against the use of physostigmine is that it has a short duration of action, so that signs of toxicity recur once the effect has worn off. The literature disproves this. In a study of 45 patients treated with physostigmine, 31 (69%) only required a single dose to reverse antimuscarinic toxicity [10]. But, even if the effects did wear off quickly in all cases, physostigmine would still have value as a diagnostic agent.

Our patient ingested VPA, but there was nothing in the history to suggest that she had access to the medication. Although a serum VPA level laboratory test exists, it is not cost-effective to measure every available drug level on every ingestion. Furthermore, if a VPA level had been measured initially, it may have been low or even undetectable. Although some immediate-release formulations of VPA exist, most patients are prescribed extended-release products. Toxicity is often significantly delayed[11]. Levels may not peak for several days, so it is essential to check serial VPA levels to avoid premature "medical clearance".

Acute VPA toxicity is characterized by progressive CNS depression. Seizures have been reported. Hypocalcemia leading to QT prolongation and tetany may be observed. The most common metabolic abnormality seen in VPA toxicity is hyperammonemia [12]. One major metabolic fate of VPA is via β-oxidation, which requires carnitine to transport VPA into the mitochondrion. When endogenous carnitine stores are depleted, VPA undergoes ω-oxidation in the endoplasmic reticulum. This produces a metabolite that inhibits carbamoyl-phosphate synthase I, the enzyme that normally converts ammonia to urea. Because the enzyme is inhibited, ammonia accumulates, and patients develop symptomatic hyperammonemia.

There are several antidotes that may be used in conjunction with supportive care to treat VPA toxicity. There are numerous case reports of naloxone reversing the CNS depression seen in VPA poisoning, and it is speculated the VPA mediates some of its effects via opioid receptors [13]. Levocarnitine (L-carnitine) supplementation allows for more metabolism via β-oxidation in the mitochondrion, and it is recommended in patients with elevated VPA levels and hyperammonemia. There is no consensus on the correct

dose, but it is reasonable to start with 50 – 100 mg/kg intravenously, then 25 – 50 mg/kg every six hours until VPA levels are in the therapeutic range [14].

Normally the elimination of valproic acid cannot be enhanced by any modality, e.g. hemodialysis or urinary alkalinization. VPA is not readily-dialyzable despite its relatively small volume of distribution because it is highly protein-bound. However, in overdose, all the protein binding sites become occupied, and the free concentration of the drug rises, making it more amenable to HD. It is reasonable to consider hemodialysis in patients with VPA levels in excess of 500 mg/L. Our patient presented with signs and symptoms consistent with excessive quetiapine, which she was reported to have ingested. Physostigmine immediately reversed her delirium and allowed us to diagnose and subsequently treat her concomitant VPA poisoning. Had we withheld this reversal agent, it is possible that her quetiapine toxicity would have persisted and possibly worsened. Furthermore, her VPA toxicity would have gone unrecognized, which could have led to an expensive, inefficient diagnostic workup and significant sequelae. We recommend that physostigmine be used in cases of moderate and severe antimuscarinic toxicity as both a diagnostic and therapeutic intervention[15].

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