

No Significant QTc Interval Change in a Case of Intentional Ziprasidone Overdose

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We report the case of a 33-year old Caucasian female admitted to our facility secondary to an intentional overdose involving ziprasidone, aripiprazole, lamotrigine and alprazolam. Duration of therapy with these agents was not available. The intake history was limited due to the patient's mental state upon admission: arousable, drowsy, unable to complete verbal answers but able to follow commands. Based on information provided by the emergency room staff, police, and previous admission records, there is a long-standing history of schizophrenia and bipolar disorder. It is not known if there were previous overdosing episodes. Approximately 90 minutes prior to admission, the patient called a mental health/mental retardation (MHMR) facility and informed them she had ingested 800 mg ziprasidone, 900 mg aripiprazole, and potentially an unspecified quantity of lamotrigine. The patient did not indicate alprazolam ingestion. MHMR informed the police and the patient was transported to the emergency room. While en route, she developed abdominal pain, nausea and vomiting. Emesis occurred in transit and 100 grams of activated charcoal was administered. Following admission, emesis occurred twice. Metoclopramide and activated charcoal were administered. No respiratory distress was noted, and chest pain or difficulty breathing was denied. Past medical history included a diagnosis of hypertension; no medication for this diagnosis was available.

The admission physical exam revealed the patient to be very drowsy and unable to provide complete answers. Vitals signs were BP 130/80, pulse 108, respiratory rate 20 and temperature 96.7⁰ F. Pupils were slightly constricted but reactive to light. Tachycardia was noted with regular rhythm and no murmurs. Admission lab work included a complete blood count, chemistry profile and toxicology screening for acetaminophen, serum alcohol, and salicylates. A urine drug screen was also done to screen for phencyclidine, benzodiazepines, cocaine metabolites, amphetamines,

cannabinoids, opiates, barbiturates, and tricyclic antidepressants. It was qualitatively positive for benzodiazepines which the patient was prescribed. Quantitative serum drug levels for alprazolam, aripiprazole, ziprasidone and lamotrigine were not ordered. The acetaminophen level was less than 10; alcohol level less than 10 and aspirin level less than 1. Additional lab work was unremarkable. The patient was admitted for electrocardiogram (ECG) monitoring which showed sinus tachycardia without evidence of ST segment changes. The QTc interval was 432 milliseconds (msec). The patient's treatment course was unremarkable and the patient was stable when she signed out against medical advice less than 24 hours following admission.

Monitoring for drug-mediated QTc changes is important as prolongation may place the patient at increased risk for the development of torsade de pointes (TdP), a ventricular arrhythmia which may be fatal and is almost always preceded by a lengthened QTc interval. Blair and colleagues reported that while QTc prolongation represents the predictor of choice for lethal arrhythmias at this time, a number of problems are associated with its use¹. These problems include measurement, calculation and interpretation.

The clinical significance of QTc prolongation remains a topic for discussion in the literature². In at-risk populations, such as those with preexisting heart disease or congenital long QTc syndrome, prolongation was linked to mortality³ and an inverse correlation between survival and QTc duration⁴, respectively. Examples of specific findings such as these are often problematic when attempting to generalize to healthy populations. In addition, QTc prolongation reporting varies and may be reported in one of two ways: as an arbitrary absolute cutoff for predicting TdP vulnerability or as absolute or percentage changes in duration from baseline values. A 440 msec QTc interval was identified as a cutoff for concern in a number of studies involving both children and adults¹. Bedner and colleagues, however, reviewed the work of other authors who

concluded the risk of TdP may not increase significantly until prolongation exceeded 500 msec³. Drugs known to cause TdP share a common feature: blocking the rapidly activating component of the delayed rectifier potassium current. Arrhythmias are more likely to occur if drug-mediated QTc prolongation occurs in combination with other risk factors. Some of these risk factors include individual patient variables, such as slow metabolizers or congenital long QT syndromes, heart failure or bradycardia, electrolyte imbalances, drug overdose of drugs associated with QTc prolongation, female gender, old age, and hepatic or renal impairment^{5,6}.

The other agents involved in this case of intentional overdose were also evaluated for QT prolongation potential. Slight increases in heart rate or tachycardia have occurred in some patients taking aripiprazole. QT-interval prolongation has been infrequently reported although the safety of aripiprazole has not been evaluated in patients with preexisting cardiovascular disease or those with risk factors for TdP^{7,8}. In the case of lamotrigine, pre-market studies demonstrated a minor incidence of an increased PR interval which was not clinically significant⁹. One case of a patient who had first-degree heart block was also reported¹⁰. In the case of alprazolam-associated cardiac effects, only isolated cases of palpitations and tachycardia have been reported, and the manufacturer information reports of tachycardia and palpitations occurred in approximately 1-8% of recipients participating in short term clinical trials¹¹.

One of the primary concerns in ziprasidone overdose is the potential for QTc prolongation. Ziprasidone received a bolded warning regarding this effect, but to date a limited number of cases involving cardiac conduction problems have been reported in adults¹²⁻¹⁴. Ziprasidone is known to prolong QTc intervals in adults in a dose-related manner¹¹. The manufacturer reported an absolute prolongation of approximately 10 msec at a dose of 160 mg/day. High-dose ziprasidone, in doses ranging from 240-320 mg/day, were assessed to determine their effect on adult ECG findings. Doses in this

range did not yield statistically significant results or approach the 500 msec threshold of concern when compared to placebo¹⁵. QTc prolongation, however, was reported in another case of multiple drug overdose. The ziprasidone dose in that case report was estimated to be 5920 mg¹⁶. In our case, ziprasidone overdose was not associated with an increased QTc prolongation. Total drug exposure time in our patient is unknown.

With an emergency admission involving antipsychotic agents, neuroleptic malignant syndrome (NMS) would be another consideration in patient assessment. NMS is a rare but potentially fatal idiosyncratic condition which traditionally develops following antipsychotic drug treatment initiation. Classic presentation features include autonomic instability with hyperthermia and hypertension, muscle rigidity, delirium, and hyperpyrexia. Additional indicators may include elevated creatine phosphokinase, myoglobinuria, and progress to acute renal failure. These features were absent in our patient. In general, second generation antipsychotic agents produce lower rates of extrapyramidal symptoms (EPS) relative to conventional antipsychotics and may be less likely to induce NMS¹⁷.

Features of overdose involving polypharmacy are also considerations. The presentation of overdose with benzodiazepines, aripiprazole and lamotrigine were also reviewed. In cases of benzodiazepine overdose, the onset of central nervous system (CNS) depression may be observed within 30-120 minutes post ingestion and presents with lethargy, slurred speech, ataxia which may progress to respiratory depression¹¹. In premarketing clinical studies, accidental or intentional acute overdose of aripiprazole occurred in 7 patients; only one of two patients ingesting the largest identified amount, 180 milligrams, developed somnolence and vomiting¹⁷. Overdose experience with lamotrigine is limited. Again, CNS effects appear to be most prevalent. Somnolence, ataxia, nystagmus, transient coma and changes in muscle reflexes were reported. Other effects have included hypokalemia, ECG abnormalities of intraventricular conduction

delay, increased seizures, nausea, vomiting, and dry mouth with thick secretions¹⁸. Our patient did present with some CNS impairment and experienced vomiting. No potential drug–drug interactions were identified with the overdose agents.

If use of an antipsychotic agent with QTc prolongation is warranted, safeguards to reduce the risk of untoward effects in cases of overdose should be considered in the treatment strategies. Potential safeguards include avoiding or minimizing concurrent usage of other drugs with QTc prolongation potential or cardiac effects. If this cannot be avoided, limiting the number of doses prescribed at one time should also be considered. Additional safeguards may include monitoring for electrolyte disturbances, as well as evaluating hepatic and renal functions. Clinicians should always obtain a resting heart rate and complete medication history, when possible, to identify concurrently prescribed medication which may be associated with QTc prolongation in addition to potent cytochrome P450 inhibitors which may contribute to an increased potential for drug-drug interactions.

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