Annals of Clinical Psychiatry, 16:229–231, 2004

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230490522061

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Pediatric Case Report of Quetiapine Overdose and QTc Prolongation

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Background. ***Consideration of the risk of QTc interval prolongation associated with atypical antipsychotic administration is mounting, as this can lead to sudden cardiac death.***

Methods. ***This is a case report of a 14-year-old boy with a history of major depressive disorder with psychotic features, post-traumatic stress disorder, oppositional defiant disorder, and polysubstance abuse who ingested 1900 mg of quetiapine.***

Results. ***One and one half hours after ingestion, the QTc interval lengthened from 453 msec to 618 msec on the printout (manual calculation was 444 msec to 500 msec, respectively). On the baseline EKG, the QTc interval was 411 msec (manual calculation of 416 msec).***

Conclusion. ***This report presents an association between higher doses of quetiapine, resulting in higher serum levels and QTc interval prolongation. Also, this report demonstrates the importance of manually calculating the QTc interval to ensure accuracy of the measurement. A review of the literature revealed two case reports and a study where quetiapine was associated with an increase in QTc interval. Further studies are necessary to understand the relationship between higher doses of quetiapine, resulting in higher serum levels, and the propensity for QTc interval prolongation to ensure safe clinical use of this medication.***

Keywords EKG; QTc interval; Atypical antipsychotics; Quetiapine fumarate; Overdose.

INTRODUCTION

We report the case of a 14-year-old male with a history of major depressive disorder with psychotic features, post-traumatic stress disorder, oppositional defiant disorder and polysubstance abuse who overdosed on quetiapine fumarate while on an acute inpatient adolescent psychiatry ward. This patient had been refractory to many previous medication regimens including olanzapine, risperidone, fluoxetine, sertraline and escitalopram during prior admissions. On this admission, the patient was being treated with the following medication regimen: quetiapine fumarate 100 mg BID and 500 mg QHS, mirtazipine 15 mg QHS and quetiapine fumarate 50 mg every two hours as needed for anxiety/agitation not to exceed 800 mg/day. The target symptoms in this patient were depression and psychosis which manifested as dissociative hallucinations. This 5′7, 73 kg young man had no significant medical history of cardiac, pulmonary, gastrointestinal or neurological disease. Allergies in this patient were to prelone and insect bites. Admission EKGs obtained approximately 14 days and 2.5 months prior to this overdose demonstrated a normal sinus rhythm and a QTc of 411 msec (manually checked with Bazett's equation was 416 msec). On hospital day #14, unbeknownst to staff, the patient ingested 19 (100 mg) quetiapine fumarate tablets that he had been hoarding (total 1900 mg, 26 mg/kg) as a suicide attempt. Approximately 30 min–1 hour later the patient reported to staff that he had overdosed, at which time an EKG was obtained that demonstrated a QTc interval of 453 msec on the EKG printout and 444 msec by manual calculation. The patient was responsive and conscious with no alterations in mental status. No neurological changes were evident on exam. As well, the patient did not complain of palpitations or dizziness. The patient's vital signs were the following: temperature 98.4 degrees, lying blood pressure 110/60 and pulse 96, standing blood pressure 124/68

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and pulse 128, respirations were 18. The patient was orthostatic by pulse. The patient did not have any acute rashes or respiratory distress. No significant findings on physical exam were present. A second EKG was obtained approximately 40 minutes after the first, which demonstrated a QTc interval of 618 msec on printout and when manually checked revealed a QTc of 500 msec, with u-waves noted in leads V2–V3. Consequently, the patient was transferred to the pediatric ICU for further monitoring and 60 g of charcoal was administered. Six hours later the QTc interval was 436 msec on printout, and was calculated the same manually, with no further elevations. Potential sequelae of this overdose such as arrhythmias, seizure activity or alterations in mental or physical functioning were not observed. Laboratory studies, including metabolic and liver panels, were within normal limits. However, it was noted the patient was neutropenic with a white count of 3.8, 43% neutrophils; the remainder of the CBC and differential was within normal limits. A CBC obtained the day prior showed WBC of 4.7, 44% neutrophils. The patient was monitored in the pediatric intensive care unit for approximately 24 hours and then re-admitted to psychiatry for further treatment. The QTc interval remained below 450 msec and the patient maintained a normal sinus rhythm throughout the duration of hospitalization in the intensive care unit.

DISCUSSION

Emerging concerns exist regarding the safety of the atypical antipsychotics, specifically the potential for QTc interval prolongation, which can lead to Torsades de pointes and sudden cardiac death. The QT interval is a measurement of the onset of ventricular depolarization and the completion of repolarization whereas the QTc interval corrects this measurement for heart rate (1). A prior study addressed these concerns (2,3) by investigating QTc interval prolongation when atypical and typical antipsychotics were given with and without metabolic inhibitors of their respective cytochrome P-450 substrates. Specifically, the ability of ziprasidone, risperidone, olanzapine, quetiapine, thioridazine and haloperidol to prolong the QTc interval was examined in the presence and absence of cytochrome P-450 metabolic inhibitors: 2D6 (paroxetine), 3A4 (ketoconazole), and 1A2 (fluvoxamine). The study population consisted of 164 subjects with a mean age of 37.1 years for men and 38.8 years for women. Of these 164 subjects, approximately three quarters were young men with schizophrenia with no history of cardiac disease and normal EKGs. Maximum dosing ranges for each atypical antipsychotic were consistent with that which was recommended in the U.S. Package Insert. The dosing ranges were the following: ziprasidone 20–80 mg BID, risperidone 1–8 mg BID, olanzapine 5–20 mg QD, quetiapine 25–375 mg BID, thioridazine 25–150 mg BID, and haloperidol 2 to 15 mg QD. Risperidone was the only atypical measured with an additional dose (6–8mg/day), resulting in administration up to 16 mg/day (2,3).

Thioridazine and ziprasidone showed the greatest QTc interval increase in the absence of a metabolic inhibitor with interval changes of 35.6 msec and 20.3 msec respectively (2,3). The administration of a metabolic inhibitor did not further prolong the QTc interval for these medications (QTc intervals with inhibitor for thioridazine and ziprasidone were 28.0 and 20.0 respectively), supporting the notion that higher serum levels are not associated with a worsening of the QTc interval.

Previous studies of the pharmacodynamics and pharmacokinetics of quetiapine fumarate demonstrate rapid absorption after oral administration, reaching peak concentrations in approximately 1.5 hours (4). Also, quetiapine fumarate is extensively liver metabolized via cytochrome P450 3A4 sulfoxidation and oxidation, rendering both metabolites pharmacologically inactive (4). The mean elimination half life of quetiapine fumarate is 2–3 hours and the pharmacokinetics were proportional to dose and similar in adolescents and adults (4).

In the aforementioned study, quetiapine was administered at 750 mg/day in the presence of ketaconazole 400 mg/day (3A4 inhibitor) which resulted in four fold increases in quetiapine plasma concentrations (2,3). This resulted in the largest reported degree of increase in QTc interval measurements (14.5 to 19.7 msec) when compared to ziprasidone, risperidone, olanzapine, thioridazine and haloperidol administration with their respective metabolic inhibitors. This increase in QTc interval closely approximates that of ziprasidone administered without a metabolic inhibitor (20.3 msec). It was found that the quetiapine and ketoconazole administration also resulted in mean heart rate increase of 15.1 bpm.

It is based on these findings that the following case report is of importance. This report suggests that higher doses of quetiapine, leading to higher serum levels, may result in QTc interval prolongation. This report also acknowledges that quetiapine fumarate may cause significant QTc interval prolongation in even a mild overdose. The U.S. Package Insert for quetiapine fumarate reports clinical studies of maximum dosing to 750 mg/day (5). In one of the placebo-controlled 6-week clinical trials it was noted that only the high dose quetiapine fumarate group (up to 750 mg/day with a mean dose of 500 mg/day) demonstrated clinical improvement in BPRS psychosis cluster when compared to lower doses (up to 250 mg/day) (5). It is common in clinical practice for psychiatrists to prescribe quetiapine up to 1000–2000mg/day to achieve clinical improvement in psychotic symptoms although no data is yet published to support this strategy. It is then of significance that 1900 mg of quetiapine fumarate (approximately 2.5 the maximum clinical dose per the package insert) caused a QTc interval prolongation >450 msec.

Significant risk for sudden death and Torsades de pointes occurs at QTc intervals >0.500 sec (6). Specifically, a review of the literature was published that identified cases of Torsades

de pointes in cases related to non-cardiac drug use, and of these cases, 92% with QTc intervals of greater than 500 msec resulted in Torsades de pointes (6). Also, in a review by Haddad, et al., it was stated that antipsychotic related QTc prolongation resulting in an absolute value of >500 msec or an increase of 60 msec from baseline resulted in increased risk of Torsades de pointes (1). It has been suggested that pharmacotherapy should be withdrawn if the QTc interval exceeds >500 msec (7).

A review of the literature yielded 2 other case reports of quetiapine overdose and QTc prolongation. The first case report was that of a 19 year old male who ingested about fifty 200 mg tablets of quetiapine, while on maintenance medications including fluvoxamine and clonazepam, and experienced significant sequelae, including unresponsiveness with a Glasgow Coma Scale (GCS) of 6 (8). At two hours post-ingestion, this patient's QTc interval was 518 msec which rose to a maximum of 710 msec at about 14 hours and then normalized to 440 msec at 27 hours post-ingestion (8). A second case report was that of 31-year-old Caucasian female who ingested 2000 mg of quetiapine, while on maintenance medications including risperidone, venlafaxine, topiramate and clonazepam (9). The patient was asymptomatic in light of a QTc interval of 537 msec immediately post-ingestion, while EKGs done at 11.2 hours and 18 hours yielded QTc intervals of 489 and 401 msec respectively (9).

Upon further review of the literature, a case report regarding a 50-year-old female that after an increase in quetiapine from 300 mg/day to 400 mg/day was found to have a QTc interval prolongation of 480 msec (10). Serial EKGs done daily for 5 days following this revealed QTC intervals from 407–421 msec (10). This patient was obese and had a past medical history significant for congestive heart failure, chronic obstructive pulmonary disease and obstructive sleep apnea. Of greater significance, however, is that the EKG printout measured the QTc interval to be 612 msec, but a manual check revealed an interval of 480 msec (10). This discrepancy between machine and manually calculated QTc intervals, similar to this case report, was due to the presence of a u-wave (10). This case report emphasized the importance of manually calculating QTc intervals to assure accuracy. In our report, even in the presence of the u-wave, the patient did have QTc prolongation compared to baseline; however the printout was inaccurate in measuring the extent of this prolongation.

The prior study (2,3) demonstrated that amongst ziprasidone, risperidone, olanzapine, thioridazine and haloperidol; quetiapine fumarate demonstrated the largest degree of increase in QTc interval prolongation when co-administered with a metabolic inhibitor. There are two previous case reports of quetiapine overdose and one case report of quetiapine administration of 400 mg/day resulting in QTc interval prolongation. This report demonstrates the importance of calculating the QTc interval manually to assure accuracy, as the printout cannot account for aberrations such as u-waves. This case report also suggests that quetiapine fumarate may cause significant increases in the QTc interval at doses only approximately 2.5 times greater than the maximum clinically tested dose. Further studies are warranted to demonstrate the relationship between oral dosing, plasma concentration and QTc interval prolongation to establish safety guidelines for the use of quetiapine fumarate. In the psychiatric patient population where overdose is of great concern, it is prudent for the physician to be aware of the therapeutic index of all prescribed medications. Therefore, significant consideration of the risks and benefits must be taken into account when selecting medication regimens for patients. This case report as well as the aforementioned study (2,3) demonstrates that perhaps greater caution should be taken when prescribing quetiapine fumarate for patients at risk for overdose as well as for patients requiring higher doses for clinical improvement. The risk for QTc interval prolongation at these higher doses of quetiapine fumarate, resulting in higher plasma concentrations, could result in fatal ventricular arrhythmias.

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