

Evaluation of the Safety of Quetiapine in Treating Delirium in Critically Ill Children: A Retrospective Review

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Abstract

Objective: Quetiapine is an atypical antipsychotic that has been used off-label for the treatment of intensive care unit (ICU) delirium in the adult population, with studies demonstrating both efficacy and a favorable safety profile. Although there is a potential role for quetiapine in the treatment of pediatric ICU delirium, there has been no systematic reporting to date of safety in this patient population.

Methods: Pharmacy records were used to identify 55 consecutive pediatric ICU patients who were diagnosed with delirium and received quetiapine. A comprehensive retrospective medical chart review was performed to collect data on demographics, dosing, and side effects.

Results: Fifty patients treated between January 2013 and November 2014 were included, and five patients were excluded from the study. Subjects ranged in age from 2 months to 20 years. Median daily dose was 1.3 mg/kg/day, and median duration of treatment was 12 days. There were three episodes of QTc prolongation that were clinically nonsignificant with no associated dysrhythmia: Two resolved over time without intervention, and one resolved with decrease in quetiapine dosage. There were no episodes of extrapyramidal symptoms or neuroleptic malignant syndrome.

Conclusions: In this population of critically ill youth, short-term use of quetiapine as treatment for delirium appears to be safe, without serious adverse events. Further research is required to assess efficacy and evaluate for long-term effects. A prospective, randomized, placebo-controlled study of quetiapine in managing pediatric delirium is necessary.

Introduction

DELIRIUM, DIAGNOSED BY the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (DSM-5) criteria, is an acute and fluctuating change in awareness and cognition that is the direct physiologic consequence of an underlying medical condition (American Psychiatric Association 2013). Delirium has recently been recognized as a prevalent and serious complication of pediatric critical illness, and has been linked to increased time on mechanical ventilation, and increased hospital length of stay (Smith et al. 2013; Schieveland and Janssen 2014; Silver et al. 2015). In adults, intensive care unit (ICU) delirium is associated with higher

mortality, long-term cognitive impairment, and dramatically higher medical costs (Milbrandt et al. 2004; Pisani et al. 2009; Girard et al. 2010; Saczynski et al. 2012; Van den Boogaard et al. 2012; Barr et al. 2013; Klein Klouwenberg et al. 2014).

The etiology of pediatric delirium is multifactorial. It is often triggered by the underlying disease, exacerbated by the iatrogenic effects of treatment, and compounded by the unusual environment of the critical care unit (Schieveland et al. 2007; Creten et al. 2011; Smith et al. 2013). As an example, consider a 4-year-old child admitted with sepsis. The systemic inflammation causes delirium, which is worsened by the sedation given for the placement of invasive lines, and then further aggravated by the sleep deprivation and prolonged bed rest.

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Funding: This investigation was supported by the Department of Pediatrics at Weill Cornell Medical College. Dr. Traube has grant support from the Empire Clinical Research Investigator Program and Cures Within Reach. Drs. Traube and Joyce have grant support from The Gerber Foundation. These funding bodies did not support this study, and had no role in the study design, data analysis, or manuscript preparation.

Availability of Supporting Data: Data described in the manuscript can be made available to any scientist wishing to use them for non-commercial purposes, with removal of all patient identifiers in order to maintain patient confidentiality.

At the Weill Cornell Center of New York Presbyterian Hospital, we have implemented routine delirium screening as standard of care in the pediatric intensive care unit (PICU). We use the Cornell Assessment of Pediatric Delirium (CAPD), a rapid and reliable observational tool scored by the bedside nurse, to detect delirium in children of all ages. This tool has been previously validated, with an overall sensitivity of 94.1% and a specificity of 79.2% in pediatric patients, with a large proportion of those studied <2 years of age (Traube et al. 2014). When a child screens positive and the diagnosis is confirmed by the treating physician, we employ a comprehensive treatment approach.

The foundation of treatment is identifying and addressing the underlying etiology. Patients are assessed for new infection or hypoxemia, pain control is optimized, sedation minimized, and withdrawal is treated. Iatrogenic factors are reduced as much as possible by avoiding anticholinergics and restraints, encouraging early mobilization, and clustering care to allow for uninterrupted sleep. Attempts to optimize the environment of care include the creation of a quiet, well-lit space with familiar objects from the child's home. When these interventions are not sufficient, pharmacologic management of delirium symptoms may be indicated (Meagher 2001; Turkel et al. 2012; Turkel and Hanft 2014).

There are currently no United States Food and Drug Administration (FDA) approved medications to treat delirium in either adults or children (Barr et al. 2013). Antipsychotics are often used to mitigate symptoms, improve cognition, and alleviate distress (Silver et al. 2010). Over the past several years, our unit's pharmacologic agent of choice has become quetiapine, an atypical antipsychotic with a favorable safety profile (Traube et al. 2013, 2014). This is off-label usage of an FDA-approved drug with respect to both the indication (delirium) and the patient population (children <10 years of age) (Quetiapine [Seroquel] [package insert]). There is growing evidence to support the safe use of quetiapine in the management of adult ICU delirium (Sasaki et al. 2003; Devlin et al. 2010; Tahir et al. 2010). Case reports, case series, and retrospective reviews have reported the efficacy of quetiapine in the management of pediatric delirium in the ICU (Silver et al. 2010; Turkel et al. 2012; Traube et al. 2013), but there has been no systematic report of safety in this patient population. In this retrospective chart review, we describe our experience with 50 consecutive patients with delirium who were treated with quetiapine over a 22 month period, with a focus on safety and potential adverse effects.

Materials and Methods

This study was conducted in the PICU at a large, urban, tertiary care academic medical center. Inclusion criteria were: Hospitalization in the PICU during the study period, diagnosis of delirium, and initiation of quetiapine for management of delirium. A list of the medical record numbers of all patients who received quetiapine over the previous 22 months was generated through pharmacy dispensing records. Demographic and clinical data were obtained on patients for the first 10 days after initiation of quetiapine. Data included age, diagnoses, Pediatric Index of Mortality scores, daily quetiapine doses, documented adverse effects, recorded QTc intervals, and use of other medications known to prolong the QTc. Charts were evaluated for the presence of symptoms that would suggest neuroleptic malignant syndrome (NMS) (combination of fever, sweating, autonomic dysfunction, and muscular rigidity) and extrapyramidal symptoms (EPS) (muscle spasms and irregular jerky movements). Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Weill

TABLE 1. PATIENT DEMOGRAPHICS

Median age (range)	4.5 years (2 months-20 years)
Male	54
Preexisting developmental delay	34
Admission diagnosis	
Respiratory insufficiency/failure	48
Neurologic	26
Hematologic/oncologic	8
Infectious/inflammatory	8
Renal/metabolic	6
Cardiac disease	4
Pediatric Index of Mortality II, median (IQR)	1.6% (1.2–4.8%)

Values represented as percentages unless otherwise specified IQR, interquartile range.

Cornell Medical College. REDCap is a secure, web-based application designed to support data capture for research studies, providing an intuitive interface for validated data entry, and audit trails for tracking data manipulation and export procedures (Harris et al. 2009). This study was approved by the Institutional Review Board at Weill Cornell Medical College, which waived the requirement for informed consent in this retrospective chart review.

Results

A total of 50 patients treated with quetiapine between January 2013 and November 2014 were included in analysis. Five children were excluded: three patients were on quetiapine at baseline (prior to admission), and two patients were prescribed quetiapine for sleep disturbance rather than delirium. A summary of patient characteristics is presented in Table 1. Median patient age was 4.5 years; ages ranged from 2 months to 20 years. Fifty-four percent of patients were male ($n=27$). Thirty-four percent of patients had underlying developmental delay ($n=17$). Admitting diagnoses were grouped into categories with the majority of patients admitted for respiratory insufficiency ($n=24$). The median Pediatric Index of Mortality II probability score was 1.6%, with an interquartile range (IQR) of 1.2–4.8%.

Patients were treated with quetiapine for a median of 12 days, with an IQR of 4.5–22 days. The median daily dose of quetiapine was 1.3 mg/kg/day, with an IQR of 0.4–2.3 mg/kg/day, and a total range of 0.2–7 mg/kg/day (Table 2). There were >2400 total doses of quetiapine administered, with >950 in children <2 years of age.

All patients were maintained on continuous telemetry for the duration of their PICU stay. There were no clinically significant episodes of dysrhythmia. Sixteen patients had electrocardiograms (ECGs) performed within the first 7 days after initiation of

TABLE 2. CLINICAL PARAMETERS OF QUETIAPINE USE AND ADVERSE OUTCOMES

Length of quetiapine use, median days (IQR)	12 (4.5–22)
Quetiapine dosage, mg/kg/day, median (IQR)	1.3 (0.4–2.3)
Number of doses administered in this review	2428
Number of doses administered to children <2 years of age	953
Episodes of prolonged QTc	3
Episodes of torsades de pointes	0
Episodes of extrapyramidal symptoms	0
Episodes of neuroleptic malignant syndrome	0

IQR, interquartile range

TABLE 3. DESCRIPTION OF PATIENTS WITH PROLONGED QTc

	<i>Demographic information</i>	<i>QTc (msec)</i>	<i>Quetiapine dose</i>	<i>Other QTc prolonging medications</i>	<i>Intervention</i>	<i>Outcome</i>
Patient 1	Toddler with respiratory failure in the setting of a viral infection	466	4 mg/kg/day	None	None	Repeat QTc 382
Patient 2	School-age child with history of bone marrow transplant, and severe hypoxemic respiratory failure	548	3.3 mg/kg/day	Ondansetron	None	Repeat QTc 498. Patient died prior to next assessment after parents requested withdrawal of support.
Patient 3	Adolescent with respiratory failure in setting of asthma exacerbation	456	6.3 mg/kg/day	None	Reduction of dose	Repeat QTc 437 on weaning dose of 4.5mg/kg/day

quetiapine. There were three instances of prolonged QTc; these three patients were followed closely with repeat ECG assessments. QTc prolongation resolved with repeat ECG assessment in two of the three. The third patient died secondary to withdrawal of life support prior to repeat assessment (Table 3). There were no patients with torsades de pointes, EPS, or NMS.

Discussion

Pediatric delirium represents a significant clinical entity in the PICU, with morbidity both in the acute phase, and a concern for deleterious long-term effects, including behavioral changes and cognitive impairment (Milbrandt et al. 2004; Pisani et al. 2009; Girard et al. 2010; Van den Boogaard et al. 2010; Saczynski et al. 2012; Barr et al. 2013; Klein Klouwenberg et al. 2014). The ability to recognize delirium in the pediatric population has been improved by the development of bedside screening tools (Smith et al. 2011; Traube et al. 2014). Based on adult literature, nonpharmacologic strategies have been designed for use in the pediatric patient, but there remains a lack of evidence for pharmacologic treatment when these measures fail (Meagher 2001). Multiple central nervous system pathways have been implicated in the development of delirium, including dopaminergic, serotonergic, glutaminergic, and cholinergic pathways in the cerebral cortex, striatum, substantia nigra, and thalamus (Pavlov et al. 2003; Gunther et al. 2008). This makes pharmacotherapy with psychoactive agents, particularly quetiapine, a physiologically reasonable choice.

Quetiapine pharmacology

Quetiapine belongs to the atypical (or second-generation) class of antipsychotic drugs. It exerts its therapeutic effects by antagonizing both dopamine D2 receptors and serotonin 5-HT2 receptors. Quetiapine also antagonizes several other receptors, including serotonin 5-HT1A, dopamine D1, histamine H1, and α 1 and α 2 receptors. Notably, it does not antagonize muscarinic or benzodiazepine receptors. Quetiapine undergoes oxidative metabolism to an active metabolite, norquetiapine, which exhibits a high affinity for muscarinic M1 receptors. Notable pharmacokinetic parameters are described in Table 4 (Devane and Nemeroff 2001; Patteet et al. 2012).

Quetiapine has been studied for the treatment of ICU delirium in the adult population. Devlin et al. evaluated the use of quetiapine for the management of ICU delirium in 36 adults in a prospective, randomized, placebo-controlled trial. Patients were randomized to receive either active quetiapine or placebo, and were allowed the use of as-needed doses of haloperidol to control breakthrough delirium. The authors reported that quetiapine treatment was associated with a significant reduction in the time to first resolution of delirium, as well as a decreased duration of delirium (Devlin et al. 2010). As a result of this promising trial, the Society of Critical Care Medicine's Guidelines for the Management of Pain, Agitation, and Delirium have incorporated quetiapine into their recommendations, and state that atypical antipsychotics may decrease the duration of delirium (Barr et al. 2013).

Safety and potential adverse effects

Quetiapine is FDA approved for the treatment of bipolar disorder, major depressive disorder, and schizophrenia in adults (Quetiapine [Seroquel] [package insert]). Quetiapine is also FDA approved for treatment of bipolar disorder and schizophrenia in children and adolescents (Findling et al. 2012; Pathak et al. 2013; Politte and McDougale 2014). In the pediatric population, common adverse events include drowsiness, agitation, orthostatic hypotension, and anticholinergic effects (such as dry mouth and constipation). Adverse effects with chronic use include a metabolic syndrome consisting of weight gain, hypercholesterolemia, and hyperglycemia (Goren and Levin 1998; Timdahl et al. 2007).

Less common but more concerning adverse effects include EPS, NMS, and prolongation of the QTc interval, with risk for torsades de pointes (Timdahl et al. 2007). Quetiapine has a significantly better EPS risk profile than other commonly used antipsychotics, including haloperidol, risperidone, and chlorpromazine (Timdahl et al. 2007). NMS is rarely described with quetiapine, and has been reported with similar frequency to placebo ((Timdahl et al. 2007; Correll et al. 2011). Among the class of atypical antipsychotics, quetiapine is one of the least likely to prolong QTc; trials have shown a prolongation of 14.5 ms on high doses at steady state (Goren and Levin 1998; Zeldox 2000; Glassman and Bigger 2001;

TABLE 4. PHARMACOKINETIC PROPERTIES OF QUETIAPINE

<i>Absorption</i>	<i>Time to peak</i>	<i>Elimination half life</i>	<i>Bioavailability</i>	<i>Metabolism</i>	<i>Elimination</i>
Rapid following oral administration	0.5–3 hours	5.3 hours	100%	Hepatic metabolism via CYP3A4 to active and inactive metabolites	Majority via urine

Correll et al. 2011; Caccia 2013). Additionally, a study evaluating the association between antipsychotic agents and cardiac outcomes found that quetiapine carried a substantially lower risk of cardiac death and ventricular arrhythmias than other typical and atypical antipsychotics (Leonard et al. 2013). These data demonstrate the relative safety of quetiapine in the general population.

Studies in adults evaluating the use of quetiapine as treatment for ICU delirium revealed a favorable safety profile. When compared with those receiving placebo, patients receiving quetiapine experienced no difference in episodes of QTc prolongation. Investigators also found no episodes of EPS or NMS in either the placebo or quetiapine groups (Sasaki et al. 2003; Devlin et al. 2010; Tahir et al. 2010).

Until now, there have been no studies systematically evaluating the safety of short-term quetiapine use in pediatric patients for the purpose of treating ICU delirium. Our retrospective review of 50 patients demonstrates an overall favorable safety profile. Although there were three cases of prolonged QTc upon initiation of therapy, none was found to be of clinical significance. Of the two patients for whom there was follow-up, one self-resolved, and the other resolved with a 20% decrease in quetiapine dosage. There were no instances of ventricular dysrhythmias, EPS, or NMS.

Dosing

Given the lack of data describing the use of quetiapine for management of delirium in critically ill children, our approach is extrapolated from the available adult data. Devlin et al. initiated quetiapine therapy at 50 mg twice a day and increased the dose based on as-needed haloperidol requirements, with a median and maximum dose of 110 mg and 200 mg per day respectively (Devlin et al. 2010). Sasaki et al. initiated therapy at either 25 or 50 mg per day with a range of 25–100 mg per day, and Tahir et al. reported initiating at 25 mg per day and increasing to a maximum of 175 mg per day (Sasaki et al. 2003; Tahir et al. 2010). Based on this adult literature, combined with the pediatric parameters for dosing quetiapine for indications other than delirium, we initiate therapy in our PICU at 1.5 mg/kg/day, administered as three divided doses. When required for breakthrough agitation, we allow for extra 0.5 mg/kg doses in addition to the standing every-8-hour regimen. Dose escalation is based on reassessment of the patient's condition. In our PICU, dosage is usually limited to a maximum of 6 mg/kg/day.

Study strengths and limitations

The major strength of this study is the inclusion of patients as young as 2 months of age, suggesting that quetiapine can safely be used in this at-risk population, and across the spectrum of pediatric ages. Although ECGs were not available on all patients, every patient admitted to the PICU was maintained on continuous telemetry, allowing us to definitively state that there were no instances of clinically significant arrhythmias. Dosing information was taken directly from the electronic medical record, ensuring accuracy and completeness, and drug interactions with other QTc-prolonging agents were accounted for. Limitations of this study include its retrospective nature, relatively small sample size, data from only a single institution, and no assessment of efficacy in this study design.

Conclusions

This retrospective chart review suggests that quetiapine is a safe drug for short-term use in even the youngest of children. With >2400 doses administered in this study, there were no instances of

clinically significant dysrhythmia, NMS, or EPS. Further study is needed to systematically assess efficacy, pharmacokinetics, optimal dosing, and long-term effects.

Clinical Significance

To date, there is no FDA-approved medication for the treatment of pediatric delirium. Quetiapine represents a possible pharmacologic agent; however, use remains limited because of its potentially serious adverse effects. To our knowledge, this study represents the largest systematic evaluation of the side-effect profile of quetiapine in this patient population. It is a necessary first step in allowing us to evaluate the efficacy of quetiapine for the treatment of pediatric delirium in future studies. A prospective double-blinded placebo controlled trial of quetiapine is needed before adoption of quetiapine as routine treatment for management of pediatric delirium.

Disclosures

No competing financial interests exist. Drs. Joyce, Witcher, and Traube participated in study design, data collection, data analysis, and drafting of the manuscript. Drs. Herrup and Kaur participated in data collection. Drs. Mendez-Rico, Silver, and Greenwald participated in study design and editing of the manuscript. All authors read and approved the final manuscript.

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