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Quetiapine as treatment for delirium in critically ill children: A case series

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Abstract. Delirium occurs in a substantial number of critically ill children and may contribute to increased hospital length of stay, and short- and long-term morbidity. Children with delirium may benefit from early pharmacologic treatment. In this case series, we describe four critically ill children, ranging from eight months to 14 years of age, who were prescribed quetiapine as treatment for delirium. In all four patients, delirium improved within 24 hours of initiation of quetiapine. With proven efficacy in adults with delirium, an established track record in children for indications other than delirium, and a favorable safety profile, quetiapine may be a therapeutic option in treating delirium in critically ill children. The time has come for a prospective, blinded study of quetiapine as treatment for pediatric delirium.

Keywords: Delirium, pediatrics, critical care, treatment, quetiapine

1. Introduction

Delirium, defined as an acute and fluctuating change in mental status with altered cognition and consciousness, is a common occurrence in critically ill adults with serious long-term consequences [1–3]. The Society of Critical Care Medicine has recently published clinical practice guidelines that call for widespread screening to detect delirium in adults, and recommends treatment to decrease duration of delirium, and ameliorate its long-term effects [4]. The cornerstone of pharmacologic therapy for delirium in adults is antipsychotics, both typical and atypical [5–7].

A growing body of pediatric literature suggests that delirium is a serious and under-recognized problem in critically ill children, as well [8–11]. Little research has focused on optimal treatment. In our pediatric intensive care unit (PICU), located in an urban tertiary-care academic medical center, we screen for delirium twice daily using the Cornell Assessment for Pediatric Delirium (CAPD), an eight-item Likert-type observational scale administered by the bedside nurse [12]. The patients described in this series screened positive for delirium with the CAPD, and then were evaluated by a child psychiatrist who diagnosed delirium after careful evaluation using the gold-standard Diagnostic and Statistical Manual of Mental Disorders (fourth edition) diagnostic criteria [1]. Other causes of altered mental status, including pain, inadequate sedation, oversedation, and acute psychiatric illness were excluded prior to confirming diagnosis of delirium.

Quetiapine, an atypical antipsychotic with a favorable side-effect profile, has been shown effective for treatment of delirium in critically ill adults. Devlin et al. [13] conducted a trial of 36 adult intensive care unit patients

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with delirium randomized to receive quetiapine 50 mg every 12 hours or placebo. The use of quetiapine was associated with significantly shorter time to first resolution of delirium, and reduced duration of delirium [13]. Quetiapine has never been formally studied for treatment of pediatric delirium. In this series, we describe our experience with using quetiapine in four critically ill children of varying ages. Our Institutional Review Board reviewed this report and waived the need for approval.

2. Case Reports

2.1. Case 1

"Sam" is an eight month old previously healthy boy admitted to the PICU with respiratory failure. Bronchoscopy showed that he had *Pneumocystis jirovecii* pneumonia. Subsequent immunologic studies indicated an atypical variant of severe combined immunodeficiency. He developed profound hypoxemia that necessitated rapid escalation of ventilator settings. His care team described him as "impossible to sedate" despite continuous narcotic and benzodiazepine infusions. On day two of intubation, despite 8 μg/kg/h of fentanyl, and 1 mg/kg/h of midazolam, he was fighting the ventilator and thrashing in bed. His Richmond Agitation-Sedation Scale (RASS) score ranged from −3 (moderate sedation) to +3 (very agitated) over the course of the day [14]. His parents described him as "inconsolable" and "possessed". The medical team resorted to intermittent use of neuromuscular blocking agents to keep the child from self-extubating, and to prevent pneumothoraces from patient-ventilator dyssynchrony.

Three days after intubation, a comprehensive assessment for delirium was made. He was noted to have mood lability with periods of extreme irritability alternating with decreased level of interest in surroundings; he had day/night reversal and frequent fidgety movements; he did not seem to recognize his mother. He was diagnosed with delirium. In place of midazolam, he was started on dexmedetomidine at 0.2 μg/kg/h. High-dose fentanyl was replaced with lower dose hydromorphone. Non-pharmacologic interventions included situating the child in a window-bed, providing familiar music and toys, and attempting to maintain a circadian lighting schedule. Although marginally improved, his agitation persisted despite gradual up-titration of dexmedetomidine to 1 μg/kg/hr. On day four, quetiapine was initiated. He was given a dose of 1.5 mg/kg/d, divided every eight hours. Within 24 hours, delirium dramatically improved, allowing for weaning of hydromorphone infusion. With careful reassessment, quetiapine dose was titrated to effect. A larger dose was prescribed at nighttime and occasional as-needed doses given for breakthrough daytime symptoms. He began having consolidated periods of sleep. Despite high ventilator settings, he required only light sedation. He was awake and calm on the ventilator, interacting with parents and caregivers. His lungs improved, he was extubated, and discharged on quetiapine with a planned two week taper.

2.2. Case 2

"Sarah" is a 3-year-old girl with one-year-long history of respiratory symptoms, swallow dysfunction, and unsteady gait (initially attributed to chronic otitis media) who presented to her local emergency department with impending respiratory failure. Following emergent intubation, computed tomography of the head showed a posterior fossa mass consistent with pontine glioma. Her respiratory status worsened and she was diagnosed with human metapneumovirus pneumonia. She was placed on neuromuscular blocking agents to allow for escalation of mean airway pressure. Five days after intubation, she was transferred to our institution.

On arrival, she was extremely agitated despite high-dose fentanyl (5 μg/kg/h) and intermittent lorazepam (0.1 mg/kg/dose every two hours). Dexmedetomidine was initiated (0.2 μg/kg/h; escalated gradually to 1 μg/kg/h) and benzodiazepines tapered with little effect. She had a craniotomy and stereotactic biopsy, and was started on high-dose dexamethasone. Nursing notes describe her as "consistently agitated", thrashing in bed, despite further increase in opiates and dexmedetomidine. She was treated with intermittent doses of pentobarbital, propofol, and vecuronium to maintain endotracheal tube position and ventilator synchrony. Her RASS score fluctuated from −4 (deep sedation) to +3 (very agitated) [14]. On psychiatric evaluation, she was noted to have periods of inconsolability, day/night reversal, near-constant restlessness, and a delayed response to interactions. She could not sustain eye contact and her actions were rarely purposeful. She was diagnosed with hyperactive delirium and started on quetiapine at 1.5 mg/kg/d. Within 24 hours, agitation improved and she achieved consolidated sleep for the first time since admission.

The quetiapine dose was increased over the next 72 hours with daily improvement noted, allowing for

tapering of dexmedetomidine and opiate infusions. She was awake, calm, and interactive on an average cumulative quetiapine dose of approximately 8 mg/kg/d. Due to tumor compression of her brainstem, she required a tracheostomy. She was discharged home one week later, on a quetiapine taper, with plans for subtotal excision followed by adjuvant radiotherapy.

2.3. Case 3

"Steven" is a six year old boy with late diagnosis of severe aortic coarctation, admitted to the PICU after uneventful repair. Post-operative course was notable for severe hypertension, controlled with beta blockade. Two days after surgery, he became acutely disoriented, extremely agitated, and actively hallucinating. Computed tomography of the head was unremarkable, an electroencephalogram showed seizures, and magnetic resonance imaging was consistent with posterior reversible encephalopathy syndrome. Seizures resolved with fosphenytoin. Anti-hypertensive medication regimen was intensified, but continued agitation made it difficult to control his blood pressure. He had frequent hallucinations and a markedly reversed sleep cycle, with more frequent awakenings with each passing night. His RASS score fluctuated from −1 (drowsy) to +4 (combative) [14]. He continued to have waxing and waning periods of agitation, with frequent hallucinations. He tried climbing a ladder to reach the "angels" on his ceiling, and would dive out of his bed to catch the "fish" swimming around him. He was diagnosed with delirium, likely as a result of posterior reversible encephalopathy syndrome and exacerbated by ongoing hypertension. He had no response to non-pharmacologic interventions, including exposure to natural light, and favorite objects from home. Four days after surgery, he was started on quetiapine (1.5 mg/kg/d divided every eight hours) for worsening delirium. After 24 hours, he had a marked decrease in agitation and increase in sleep time. His dose was up titrated over the next three days with resolution of hallucinations and improvement in orientation and cooperation.

2.4. Case 4

"Saul" is a 14-year-old boy with relapsed acute lymphoblastic leukemia, despite stem cell transplant, with chronic respiratory insufficiency and tracheostomy dependence. He was transferred to the PICU for acute-on-chronic respiratory insufficiency, with worsening fungal pneumonia. On PICU day one, he received a bone marrow boost, fluid resuscitation, pressors and mechanical ventilation. On PICU day two, he reported feeling "confused" and "scared", and was unable to sleep. On PICU day three, he was noted be extremely withdrawn, with a flat affect. He then began having frank hallucinations, talking to his father who was not present. On psychiatric assessment, he displayed severely reduced comprehension, and psychomotor retardation. He was diagnosed with delirium, with contributing factors including cytokine storm from stem-cell infusion, and ongoing fevers. He was started on quetiapine with improvement noted that day. With up-titration of dose, he had complete resolution of delirium symptoms within 48 hours.

3. Discussion

Delirium is common in critical illness with many contributing factors [4,15]. Its complex pathophysiology is incompletely understood. Dopaminergic, serotoninergic, glutaminergic, and cholinergic pathways in the cerebral cortex, striatum, substantia nigra, and thalamus have been implicated [15]. Imbalance in the synthesis, release, and inactivation of neurotransmitters can result in altered cognitive function, behavior, and mood [2]. The underlying illness with associated inflammation and impaired oxidative metabolism is a major cause [4]. Seizures, sepsis, shock, and metabolic and electrolyte disturbances have all been associated with the development of delirium [16]. Altered sleep-wake cycles, limited social interaction, and pain play a role. Steroids, benzodiazepines, opiates, and anticholinergic agents have been implicated as well [4,14,15]. Delirium has long been under-recognized in pediatrics, likely due to the difficulty in screening for, and diagnosing this complex entity in children of varying developmental levels [8,12]. PICU patients with refractory agitation, or the withdrawn child, may in fact be delirious [8–12,17].

Atypical antipsychotics have been postulated to have a substantial role in the management of delirium, based on the wide range of receptor activity (including acetylcholine, dopamine, serotonin, and norepinephrine) as compared to typical antipsychotics (primarily dopamine) [4,6]. In addition, the traditional use of haloperidol (a typical antipsychotic) as first-line pharmacologic treatment for adult delirium has recently been called into question, with a randomized trial showing no decrease

in duration of delirium as compared to placebo [18]. Case studies and retrospective reviews have suggested a beneficial effect of atypical antipsychotics in critically ill children, specifically addressing olanzapine, risperidone, and quetiapine [19,20].

Quetiapine, an atypical antipsychotic, is a dopamine (D2) and serotonin receptor antagonist and 5-HT1A partial agonist in the central nervous system. It is metabolized by cytochrome P450 isoenzyme 3A4 (CYP3A4) into N-desalkyl quetiapine, a muscarinic M1 receptor agonist that inhibits noradrenaline reuptake. A substrate of CYP3A4, quetiapine is subject to several drug interactions. Strong inducers of CYP3A4 (such as many anti-epileptics) enhance metabolism. Strong inhibitors (such as azole antifungals) decrease metabolism [21]. Elimination half-life is approximately three and a half hours, terminal half-life seven hours, and steady state concentration achieved in two to three days. It is largely excreted in the urine but does not require dose adjustment for renal impairment [22].

Adverse effects include drowsiness, agitation, orthostatic hypotension, anticholinergic effects such as dry mouth and constipation, extrapyramidal symptoms, neuroleptic malignant syndrome, and prolongation of the QTc interval [23]. Quetiapine has a significantly better extrapyramidal symptoms risk profile than other commonly used antipsychotics, including haloperidol, risperidone, and chlorpromazine [23]. Neuroleptic malignant syndrome is exceedingly rare with quetiapine, with rates similar to placebo [23,24]. Of the atypical antipsychotics, quetiapine is one of the least likely to prolong QTc; some trials have shown an increase by 14.5 milliseconds on high doses at steady state [24–28]. Chronic adverse effects include weight gain, hypercholesterolemia, and hyperglycemia [28].

American Psychiatric Association guidelines for management of delirium recommend monitoring with a baseline electrocardiogram. Prolongation of QTc interval greater than 450 milliseconds, or increase of 25% from baseline, warrants telemetry or dose reduction. Decreased dosing should be considered when given with inhibitors of CYP3A4, or in hepatic disease [29].

Quetiapine is used widely for management of pediatric psychiatric illness. It is approved by the U.S. Food and Drug Administration for management of bipolar disorder in children ten years or older and schizophrenia in 13 years or older [30–32]. Quetiapine is used off-label, and in younger children, for the treatment of autism, psychosis, bipolar disorder, insomnia, and dangerous aggression [30,33]. Pediatric doses range from 50 to 800 mg per day, illustrating its large therapeutic profile [30–32]. Quetiapine has never been formally studied for treatment of pediatric delirium [19].

In the four cases described in this report (Table 1), starting doses averaged 1.7 mg/kg/d. Each patient required up-titration of doses over two to three days. As-needed doses of 0.5 mg/kg/dose were given for breakthrough delirium (as identified by the CAPD screen [12]), no more frequently than every six hours. Each patient required a higher nighttime dose to facilitate restoration of the disordered sleep-wake cycle. Total daily dosing, when adjusted for patients' weights, ranged from approximately 2 to 8 mg/kg/d. With initiation of quetiapine, there was a substantial decrease in requirement for narcotics and sedatives, allowing for rapid weaning of those medications. As is routine in our PICU, all children had telemetry monitoring, and QTc was measured each day. None of the children had clinically significant prolongation of QTc. In our small sample, we did not detect any adverse effects.

In conclusion, with proven efficacy in adults with delirium, an established track record in children for indications other than delirium, a favorable safety profile,

Table 1
Summary of patient data

Characteristics	Case 1	Case 2	Case 3	Case 4
Age	8 months	3 years	6 years	14 years
Gender	Male	Female	Male	Male
Weight	9 kg	12 kg	19 kg	38 kg
Diagnosis	*Pneumocystis jirovecii* pneumonia	Pontine glioma	Coarctation of aorta	Acute lymphoblastic leukemia; fungal pneumonia
Starting daily dose (divided every 8 hours)	15 mg* (1.7 mg/kg/d)	25 mg (2.1 mg/kg/d)	30 mg* (1.6 mg/kg/d)	50 mg (1.3 mg/kg/d)
Max daily dose quetiapine	20 mg (2.2 mg/kg/d)	100 mg (8.3 mg/kg/d)	100 mg (5.3 mg/kg/d)	137.5 mg (3.6 mg/kg/d)
Duration of quetiapine therapy	15 days	20 days	9 days	12 days

*Compounded by hospital pharmacy using 25-mg tablets.

and wide therapeutic window, quetiapine is a logical choice for treatment of pediatric delirium. As described in this case series, we have used it successfully in ages ranging from infancy to adolescence. Within 24 hours of initiation of quetiapine, we have seen improvement in delirium symptoms. With careful attention to symptomatology, and up-titration of dose, we have seen resolution of delirium in a matter of days. In summary, we believe that quetiapine should be considered as a therapeutic option in treating delirium in critically ill children of all ages. The time has come for a prospective, blinded study of quetiapine as treatment for pediatric delirium. Early diagnosis and treatment could yield significant improvement in clinical outcomes.

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