Olanzapine reduces delirium symptoms in the critically ill pediatric patient

Sean Sassano-Higgins*, Nicholas Freudenberg, Julienne Jacobson and Susan Turkel

Department of Psychiatry and Pediatrics, Keck School of Medicine, Children's Hospital Los Angeles, University of Southern California, Los Angeles, CA, USA

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Abstract. Delirium is a neuropsychiatric disorder characterized by acute disturbances in attention, consciousness, cognitive processing, perception, and the sleep-wake cycle. The few studies investigating treatment of delirium in critically ill children and adolescents have used differing diagnostic criteria, and have not employed control groups or procedures to blind observations. The objective of this study was to examine the efficacy of olanzapine for the treatment of delirium in the pediatric intensive care unit (ICU) using methodological procedures to reduce bias and allow greater generalization. Psychiatric records of 59 patients admitted to the pediatric ICU or cardiothoracic ICU over a 4 yr period with the diagnosis of delirium were examined. The delirium rating scale was used to assess delirium severity at the time of initial psychiatric evaluation and five days later. Raters were blinded to medication administration. Patients who were diagnosed with delirium, but did not receive olanzapine, or any other antipsychotic medication, served as the control group. Greater improvement of delirium symptoms was found for the olanzapine group ($n=31$) than the control group ($n=28$) ($F_{(1,40)}=4.86$, $r=0.33$, 95% confidence interval = 0.020–0.58). This finding remained statistically significant after controlling for initial delirium severity ($F_{(1,20)}=28.62$, $r=0.77$, 95% confidence interval = 0.50–0.90). This study demonstrates patients with delirium administered olanzapine had greater reduction of delirium symptom severity than controls. It supplements the existing literature by using a study design that reduces expectancy effects and allows examination of the natural history of delirium symptoms without medication administration.

Keywords: Olanzapine, antipsychotics, neuroleptics, delirium, pediatric intensive care

1. Introduction

Delirium is a disorder involving varying degrees of impaired attention, disturbance of consciousness, cognitive processing, perceptual disturbances, and alterations of the sleep-wake cycle. Onset of symptoms is acute, and symptom severity typically fluctuates over time [1]. Delirium is associated with a wide variety of underlying medical, surgical, pharmacologic, and traumatic etiologies, and occurs in seriously ill patients of all ages [2].

Delirium is frequently seen in adult intensive care unit (ICU) patients and other critically ill adult and geriatric patients [3–7]. It is associated with poorer long-term outcome in terms of prognosis, length of hospital stay, cognitive capacity, and mortality [3,5]. Studies using appropriate diagnostic tools, such as the delirium rating scale (DRS) [8] and confusion assessment instrument for the ICU [9], have estimated the incidence of delirium in the ICU to be greater than 80% [3]. Recent clinical practice guidelines have recommended systematic monitoring for the development of delirium in ICU patients [10].

Non-pharmacologic environmental interventions, directed at reducing confusion and providing comfort, are essential to address delirium symptoms, but may

*Corresponding author: Sean Sassano-Higgins, Department of Psychiatry, Keck School of Medicine, University of Southern California, 2010 Zonal Avenue, #1P10 (OPD), Los Angeles, CA, USA. Tel.: +1 323 226 5555; Fax: +1 323 226 7818; E-mail: Sahiggins@usc.edu.

not be sufficient when used alone [11]. Although the evidence base for effective drug interventions for delirium is limited, antipsychotics have been shown to address a range of symptoms in adult patients with delirium, and the administration of these medications has become a reasonable first line approach for the pharmacologic treatment of delirium in the adult population [12,13]. This is despite a lack of Food and Drug Administration approval, double-blind randomized clinical trials, or placebo controlled studies [4,14,15].

Few studies have investigated the treatment of delirium symptoms in pediatric populations [16–18], and current treatment approaches for children are modeled on treatment recommendations for adults [16]. A wide range of antipsychotic medication is available, however, haloperidol is the antipsychotic most often used in adult cases of delirium [19]. Atypical antipsychotics have been found to have efficacy similar to haloperidol in adults [20,21]. Haloperidol, although frequently used in children, is associated with a risk of extrapyramidal symptoms [22], and hypotension and cardiac irregularities, the risk of which may be higher in younger children [23].

The studies that have investigated delirium in critically ill children and adolescents have used differing diagnostic criteria, and have not employed control groups or procedures to blind investigators' observations, making internal validity questionable and generalization difficult [24]. The experimental evidence of safety and efficacy of atypical antipsychotics in children and adolescents for treatment of delirium is limited and inconclusive [25]. A recent systematic review concluded that current treatment practices are based on little empirical evidence [26].

The objective of this study was to examine the efficacy of antipsychotic medication for the management of delirium symptoms in the pediatric intensive care unit (PICU) population using methodological procedures to reduce bias, and to provide a comparison with a non-medicated control group with delirium, allowing for greater generalization to the critically ill pediatric population. At the institution where the study was performed, olanzapine was most often prescribed in this setting, and therefore was the focus of examination. Results from an uncontrolled trial suggest that olanzapine is equivalent in terms of efficacy and safety to risperidone and quetiapine in children [27].

This study was formulated to test the specific hypothesis that olanzapine administration will be associated

with a reduction in the severity of symptoms of delirium in the critically ill pediatric patient.

2. Materials and methods

The Children's Hospital Los Angeles Committee for Clinical Investigations (Institutional Review Board) approved this study.

A retrospective longitudinal study design was used. Records of patients admitted to the Children's Hospital Los Angeles PICU or cardiothoracic intensive care unit (CTICU) evaluated by psychiatry and diagnosed with delirium from January 24, 2006 to July 24, 2010 were examined. Antipsychotic medication was recommended to all patients included in this study.

Patients with the clinical diagnosis of delirium who received olanzapine to address symptoms of delirium comprised the study group. The control group was comprised of patients with the clinical diagnosis of delirium who did not receive any antipsychotic medication as part of treatment. Reasons for not administering psychotropic treatment were varied, and usually reflected parental choice. Olanzapine was the only antipsychotic medication administered to patients included in this study.

The clinical diagnosis of delirium was based on the diagnostic and statistical manual-IV-text revised criteria [1], and was made at the time of initial psychiatric consultation by the senior authors, clinicians experienced in the diagnosis of delirium. Etiology of delirium in this population was likely multifactorial, and has been discussed in detail in a prior study [26].

The DRS was administered retrospectively via chart review to assess delirium severity at the time of initial psychiatric evaluation and approximately 5 days later [8]. The validity of the retrospective use of the DRS has been demonstrated in a prior study [28]. Information regarding use of antipsychotic medication to assist with treatment of delirium was removed from the medical record to blind the researchers performing the DRS. The order of the assessment of consultation records was randomized with respect to date of consultation, initial or final consultation, and medication administration, to further decrease risk of bias. Ratings were completed by two clinicians experienced in the use of the DRS. Clinicians were trained to one-hundred percent agreement on practice cases prior to rating cases included in this study.

Olanzapine use and dosage information were compiled from clinical and pharmacy records. The starting

dosage of olanzapine was estimated clinically based on patient age, size, and recent use of other sedatives or opioids. Typical starting doses of olanzapine were 0.625 mg per oral every night (QHS) to twice daily for infants and 1.25 mg per oral QHS to twice daily for toddlers. In cases when the patient was older, larger, or extremely agitated, a scheduled starting dose of 2.5 mg to 5 mg per oral QHS to twice daily was used. In the event of persistent hallucinations, confusion, insomnia, or to control agitation and potentially dangerous behavior, additional doses of olanzapine were available on an as needed basis. Typical as needed dosing ranged from half to equal the starting dose, available every hour, with a maximum of four doses per 24 h period. A routine daily dose was established based on the amount of olanzapine required over 24 h to attain adequate symptom control. Administration of olanzapine was oral, sublingual, or via nasogastric or gastrostomy tube. No intramuscular or intravenous administration was used.

In addition to medication, all patients and families were provided support and psychoeducation about environmental interventions they could utilize/provide to maintain diurnal routine and decrease confusion. Nursing staff and family members were instructed to reorient and reassure patients frequently.

Following assessment of delirium severity, data were unblinded, and olanzapine administration was examined as a between groups variable. Severity of delirium symptoms, as measured by the DRS, was examined as the primary outcome variable. Change in delirium severity was calculated as $DRS_{\text{final evaluation}} - DRS_{\text{initial evaluation}}$. To aid interpretation, change scores were reverse coded, such that positive scores indicated greater improvement of delirium symptoms. Data were analyzed using a commercially available statistics software program [29]. Student's *t*-tests were performed for data involving single group and two group analyses. Analysis of variance (ANOVA) was performed for statistical tests involving independent variables with more than two levels. When analyses with a single degree of freedom in the numerator were conducted, the correlation coefficient, *r*, with associated confidence interval (CI), was calculated as a measure of effect size. When analyses of multiple degrees of freedom in the numerator were conducted, exact *P* values were calculated.

To remove variance in delirium severity change scores attributable to initial delirium severity, ANOVA with blocking on initial delirium severity was utilized. Initial delirium severity was recorded into six blocks based on

initial DRS scores: 0–5, 6–10, 11–15, 16–20, 21–25, and 26–30. To examine the association between age and change in delirium severity, age was recorded into five blocks: 0–1 year-old, 2–5 years old, 6–10 years old, 11–15 years old, and 16–20 years old.

3. Results

Review of consultation records showed that olanzapine was administered to 31 patients with the diagnosis of delirium admitted to the PICU or CTICU during the specified period. The control group was composed of 28 patients who were diagnosed with delirium, but did not receive antipsychotic medication.

Information regarding demographic variables, delirium severity at the time of initial psychiatric evaluation, and change in delirium severity is presented in Table 1. The olanzapine group and control group did not differ in age or sex composition. The olanzapine group had more severe symptoms of delirium at the time of initial psychiatric evaluation than the control group ($t_{(57)} = 3.11$, $r = 0.38$, 95%CI = 0.14–0.58). Delirium symptoms significantly improved over time in the olanzapine group ($t_{(30)} = 7.21$, $r = 0.80$, 95%CI = 0.62–0.90) and the control group ($t_{(27)} = 3.84$, $r = 0.59$, 95%CI = 0.28–0.79).

Results of the ANOVA based on unadjusted data are shown in Table 2. Greater improvement of delirium symptoms was found in the olanzapine group than in the control group ($F_{(1, 40)} = 4.86$, $r = 0.33$, 95%CI = 0.020–0.58).

Results of the ANOVA with blocking by initial delirium severity are shown in Table 3. The delirium severity blocking variable removed a significant portion of variance from change in delirium severity ($F_{(5,20)} = 13.06$, $P = 9.9e^{-6}$). Olanzapine remained associated with greater improvement in delirium severity relative to control

Table 1
Descriptive data and change in delirium severity

Data	Olanzapine group (n = 31)	Control group (n = 28)
Sex (male/female)	21/10	18/10
Age (mean ± SD)	9.22 ± 6.23	8.44 ± 5.98
Delirium Initial (mean ± SD)	19.13 ± 6.34	14.07 ± 6.10
Delirium Final-Initial (mean ± SD)*	9.74 ± 7.53	3.82 ± 5.27

*Reverse coded.

Table 2
Analysis of variance using unadjusted data

Variable	Sum of squares	Degrees of freedom	Mean square	<i>F</i>	<i>P</i>
Treatment	218.98	1	218.98	4.86	0.033
Age	126.59	4	31.65	0.70	0.60
Sex	43.32	1	43.32	0.96	0.33
Treatment × Age	152.19	4	38.23	0.85	0.50
Treatment × Sex	12.08	1	12.08	0.27	0.61
Treatment × Age × Sex	15.90	2	7.95	0.18	0.84
Error	1803.38	40	45.08		

Table 3
Analysis of variance with blocking by initial delirium severity

Variable	Sum of squares	Degrees of freedom	Mean square	<i>F</i>	<i>P</i>
Treatment	577.00	1	577.00	28.62	0.000031
Age	23.56	4	5.89	0.29	0.88
Sex	3.18	1	3.18	0.16	0.69
Delirium block	1316.31	5	263.26	13.06	0.0000099
Treatment × age	97.17	4	24.29	1.20	0.34
Treatment × sex	14.10	1	14.12	0.70	0.41
Treatment × age × sex	62.49	2	31.24	1.55	0.24
Error	403.17	20	20.16		

($F_{(1,20)} = 28.62$, $r = 0.77$, 95%CI = 0.50–0.90). Age and sex were not found to moderate the relationship between olanzapine and change in delirium severity.

4. Discussion

This study demonstrates that olanzapine administration is associated with a reduction in the severity of delirium symptoms in the PICU and CTICU patient. Given the findings of this study, olanzapine administration may be a useful therapy for critically ill pediatric patients diagnosed with delirium. Although the non-randomized and retrospective design of this study precludes determination of a causal relationship, this study provides less biased evidence regarding the efficacy of olanzapine to address symptoms of delirium in the critically ill pediatric population than has been previously available.

Although the olanzapine group had greater delirium symptom severity at the time of initial evaluation, analyses based upon data adjusted for initial delirium severity showed the improvement in symptoms was greater than would be expected based on improvement over time alone. It is important to note, however, that

statistical procedures are not a substitute for random assignment, and future randomized studies will be needed to provide additional evidence of olanzapine efficacy.

Age and sex were not found to moderate the relationship between olanzapine administration and improvement in delirium symptom severity, indicating that males and females of all age groups would likely respond equally well to olanzapine.

The results of this study are similar to previous studies showing efficacy of the typical [21,30], and atypical [27] antipsychotic medications in reducing delirium symptoms in the pediatric population.

No significant adverse effects associated with administration of olanzapine, including extrapyramidal signs or arrhythmia, were recognized in this study, although all antipsychotic medications carry the risk of QT prolongation and ICU patients are at increased risk of arrhythmia from electrolyte abnormalities, infection, hypoxia, or exposure to other drugs which can prolong cardiac conduction [31–33]. Olanzapine administration has also been associated with elevation of liver transaminases, which was not noted as an adverse effect in this study [34]. The lack of adverse effects associated with olanzapine in this study, and the report of adverse effects

with haloperidol by prior studies, suggests that olanzapine may be a safer treatment option than haloperidol [23,35]. However, other studies have found haloperidol and olanzapine to have relatively equivalent rates of adverse effects, and more research is needed in this area [22].

Aside from lack of randomization, two other limitations of this study are recognized. First, concurrent medication administration was not examined in this study. Benzodiazepines and opiates are widely used in the ICU and have been associated with the development of the symptoms of delirium [2]. Second, total dosage information for individual patients was not available, precluding examination of the relationship between olanzapine dose and improvement in delirium symptoms.

Ideally, randomization and a placebo-control design provide for greater control of possible confounding variables, however, this is challenging to perform in the ICU setting with severely ill patients with multiple comorbidities. This study was designed to reduce bias present in prior pediatric delirium studies, with the intention to more accurately evaluate efficacy and safety of olanzapine in the critically ill pediatric patient with delirium. Olanzapine appears to be efficacious for reducing the severity of delirium symptoms, regardless of the age or sex of the patient, and may not be associated with great frequency of adverse side effects. This study provides evidence supporting the current clinical practice of olanzapine use in pediatric ICU patients with delirium to provide symptomatic control and reduce suffering, with the goal of supporting the PICU or CTICU team while they provide essential care.

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