Review of the Pharmacological Treatment of Delirium in the Pediatric Population with Accompanying Protocol

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Abstract

Objective: To review the current state of pharmacological treatment of delirium in the pediatric population and to derive a treatment protocol from our review.

Method: Medline-assisted search of the literature. Articles pertaining to the pharmacological treatment of delirium in children and adolescents were reviewed. Due to the paucity of articles, studies of treatment guidelines for delirium in the adult population were reviewed. Also presented for reference, are studies of optimal dosing regimens of psychotrophic agents potentially useful in treating pediatric delirium. Our protocol is extrapolated from previously established guidelines for adult treatment meshed with the current knowledge presented in the literature pertaining to children and adolescents.

Results: Review revealed only one retrospective study evaluating the pharmacological treatment of delirium in children and adolescents. One anecdotal report of risperidone successfully treating delirium is presented. Intravenous haloperidol is the mainstay of pharmacological treatment in medically ill adults and haloperidol has a long history of safety and efficacy in children and adolescents.

Conclusion: Use of intravenous haloperidol with titration to an efficacious dose would be the first line approach to treat symptoms of delirium in the pediatric population. However the lack of data and systematic analysis in the literature demonstrates an acute need for structured research in this area.

The aim of this article is to review the current state of pharmacological treatment of delirium in the pediatric population and to derive a treatment protocol from our review. There is a conspicuous lack of research in this area and there are no previous reviews in the literature. To complete our objective, we present the current state of treatment of delirium in adults, along with the limited amount of literature pertaining to delirium in children and adolescents. For reference, current pediatric pharmacological dosing regimens are presented. Our protocol is derived from an extrapolation of guidelines for adult treatment meshed with the current knowledge presented in the literature pertaining to children and adolescents.

Delirium is a transient mental syndrome of acute onset, characterized by global impairment of cognitive functions, a reduced level of consciousness, attentional abnormalities, changes in psychomotor activity and a disordered sleep-wake cycle (1). The concept of delirium has been recognized for approximately 2500 years (2). The diagnostic criteria have evolved to several core features (Table 1) coupled with specifiers that distinguish etiology, i.e. due to a general medical condition, due to multiple etiologies, for substance intoxication, for substance withdrawal and causes not otherwise specified (3).

The average prevalence of delirium in the general hospital population is 20% (4). Although the pediatric population has not been well studied, Antoon et al. (5) reported that approximately 14% of hospitalized burn patients had delirium. These estimates may be low given that there is a high rate of misdiagnosis with delirium. Armstrong et al., (6) reported that 46% of hospitalized adults with delirium were misdiagnosed, i.e. a delirious patient was diagnosed with another condition (depressive disorder, psychotic disorder, no diagnosis, etc.). Also the expression of delirium in children can vary from adults, e.g. magical thinking, mania or regression (7), making the diagnosis even more difficult for the treating physicians. The transient nature of delirium also adds to the difficulty with diagnosis.

The consequences of altered consciousness can be quite deleterious to the patient, e.g. pulling out catheters and other self-injurious behavior and has been shown in adult populations to increase mortality (4,8). Thus, early recognition of the delirium with appropriate treatment is essential.

The first step in the treatment of delirium is to identify any causal condition. The most common causes involve intoxication with exogenous substances, systemic or cerebral disease and withdrawal from substances of abuse (1). However the underlying etiology may not be easily distinguished. This can be quite difficult in that the delirium may be caused by multiple etiologies and individually may not be considered significant by the treating physicians. In the interim of diagnostic work-up, treatment should include reassurance and reorientation. If this is not sufficient, pharmacological intervention is used as an adjunct for symptom management and antipsychotic medication has been the mainstay of treatment (9).

TABLE 1.

Diagnostic Criteria for Delirium

A) Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.

B) A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting condition, established, or evolving dementia.

C) The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association, 1994.

TYPICAL ANTIPSYCHOTICS

Haloperidol

Haloperidol, a butyrophenone neuroleptic that can be administered via enteral, intramuscular or intravenous routes, is a well-documented safe treatment of delirium symptoms in adults (9). It is a high potency neuroleptic with low potential for anticholinergic, antialpha-adrenergic and autonomic effects and is unlikely to exacerbate delirium (9,10). It alleviates aggression, psychomotor agitation, hallucinations and delusions (10) and is considered the preferred agent for treating delirium in the critically ill adult (11). The intravenous route has a safe side-effect profile and has a reduced incidence of extrapyramidal reactions when compared to oral administration (10,12). The intravenous route is also the quickest way to initiate treatment, i.e. peak serum levels are reached soon after administration, whereas the enteral and IM routes may take up to several hours (10). Also, parental doses of haloperidol have 100% bioavailability (compared to the approximate 60% bioavailability of oral dosing), and are dosed approximately one-half that of oral doses (10). Initial bolus intravenous doses range from 0.5 to 20 mg (4) and mega-doses (>1000 mg/day) have been given safely in cases of refractory delirium (13,14). Specific guidelines for treating the delirious adult patient vary in the literature. Shapiro et al. (11) outline a starting dose of 2 to 10 mg intravenously with the dosage repeated every 2 to 4 hrs. Maintenance dosing regimens have been proposed of continuing intravenous haloperidol at 50% of the dose that controlled symptoms with rapid dose reduction (15) or administering low dose (0.5 to 3 mg) oral haloperidol (16).

Antipsychotic medications though commonly prescribed to children are not as well investigated. The Food and Drug Administration (FDA) advertising guidelines for haloperidol indicate use in (i) management of psychosis, (ii) control of tics and vocal utterance in Tourette's disorder, (iii) severe behavioral problems in children marked by combativeness and/or explosive hyperexcitable behavior (that is not accountable to immediate provications) and short-term treatment of ADHD (17). The lower age limit is 3 years with dose limits of 0.15 mg/kg/day for psychosis and 0.075 mg/kg/day for behavior disorders and Tourette's disorder (17). However, review of the literature by Findling et al. (18) reveals that haloperidol has also been used in treating mood disorders, pervasive developmental disorder, mental retardation, conduct disorder, anorexia nervosa and personality disorders in children and adolescents. Children have been found to respond to lower neuroleptic plasma levels (19) and the dosing of haloperidol, in the pediatric population, tends to be lower and more conservative than in adults. The average optimal dose range of haloperidol for the schizophrenic pediatric population is 0.02 to 0.12 mg/kg/day [0.5 to 3.5 mg/day] (20).

The most common short-term side effects of haloperidol in children and adolescents are sedation and extrapyramidal symptoms (EPS) (21). EPS are rarely observed in preschool-aged children, but are more common in school age and adolescents (19). The sedation is dose-related and can be relieved by a reduction in dose (21). Extrapyramidal symptoms are not dose-dependent and are sudden in onset (9). Most

EPS can be resolved with a reduction in dose and/or management with anticholiner-gics (20). Also, with short-term haloperidol use, the possibility of neuroleptic malig-nant syndrome (NMS) should be considered. NMS is a potentially fatal complication that occurs at all ages and starts within a few days of initiating neuroleptic treatment. Fortunately the syndrome is rare —0.4% to 0.5% of newly treated patients (22). Also of concern, in critically ill adults, is an association of prolongation of the QTc interval (QT interval corrected for heart rate) with the possibility of ensuing torsades de pointes (a polymorphous ventricular tachycardia) with intravenous butyrophenone therapy (23,24). Lawrence & Nasraway (23) recommend electrocardiogram (EKG) monitoring in critically ill patients, with discontinuation or reduction of dose if the QTc interval lengthens by 25% or more over baseline. Cardiac conduction abnormali-ties associated with butyrophenone administration in children and adolescents have not been reported in the literature and the implications of this possible adverse effect are not known.

There has only been one study revealed in our search that addressed the use of neuroleptics to treat delirium in children and adolescents. Brown et al. (25) studied the use of haloperidol in 30 pediatric burn patients to treat agitation and delirium. Here the short term use of haloperidol (longest period of treatment was three months) had an incidence of adverse reactions of 0.47% (an episode of decreased consciousness and an episode of hypotension after 429 doses administered). The mean dose of haloperidol used was 0.047 mg/kg with the mean number of doses given at 14. The largest cumulative dose administered over a 24-hour period was 0.455 mg/kg. The largest number of doses given over a 24-hour period was six. With intravenous administration of haloperidol, the onset of effect was within thirty minutes. They reported higher efficacy via the intravenous route and found no contraindications to using haloperidol to treat agitation in children.

Droperidol

Droperidol is another butyrophenone neuroleptic that has also been used successfully to treat delirium in adults (26,27). It is available for intramuscular or intravenous administration (17). Compared to haloperidol, it has a more rapid onset of action, is more sedating and is more apt to cause hypotension (9,26). Its use to treat delirium in the pediatric population has not been reported. However, droperidol has been studied for the management of acute agitation and aggression in children and adolescents. Joshi et al. (28) reported use of intramuscular droperidol in a children's inpatient unit to control extreme aggression and violent behaviors. Over a period of three years, twenty-six children (mean age of 9.14) received a one time dose (except two boys who were refractory after 30 minutes and required another dose) of droperidol to induce sedation. The amount of droperidol used, in the children, was based on body weight: <75 lbs. = ¼ cc; 75 to 125 lbs. = ½ cc; 125 to 150 lbs. = ¾ cc; >150 lbs. = 1cc and the mean dose used was 0.437 cc (1cc = 2.5 mg). The use of droperidol was deemed efficacious and produced only mild EPS in two of the children.

ATYPICAL ANTIPSYCHOTICS

The emergence of the new atypical antipsychotics has allowed a greater arma-
ment of pharmacological choices in treating many psychiatric conditions in children.
The new medications have shown benefit without some of the extrapyramidal side
effects of the conventional antipsychotics (29–31). The atypical antipsychotics have
been used in children and adolescents in cases of schizophrenia (32,33), autism (34),
and pervasive developmental disorder (35).

Dosing regimens of the atypical antipsychotics in children and adolescents vary
in the literature. Risperidone and olanzapine are only administered enterally.
Risperidone was FDA approved in 1993 with a dosing range of 2 to 16 mg/day (17). In
children with psychotic disorders, the optimal clinical response was found at a mean
daily dose of 5.93 mg (32). In autism, response was with a mean dose of 1.3 mg/day
(34). A study of children and adolescents with pervasive developmental disorder
showed improvement of symptoms with a mean dose of 2.7 mg/day (35). The FDA
approved olanzapine in 1996 with a dosing range of 5 to 20 mg/day (17). In adults,
olanzapine has been found to posses antipsychotic properties with an optimal dosing
range of 2.5 to 15 mg/day (30). Olanzapine has not been extensively studied in
children, however, a pilot study of childhood-onset schizophrenia showed efficacy at a
mean dose of 17.5 mg/day (36). Also a study of children, adolescents and adults with
pervasive developmental disorders showed clinical improvement with a mean dose of
7.8 mg/day (37).

The literature does not document many short-term contraindications of the
newer antipsychotics in children and adolescents. Risperidone has been shown to
cause mild sedation and EPS in a population of adolescents with schizophrenia, with
the expression of EPS inversely proportionate to the rate of titration of the risperi-
done (32). There has been a case report of olanzapine (dosed 7.5 mg/day over a two to
three week period) inducing mania in a sixteen year old male (38). Also, as with the
typical antipsychotics, there is a risk of NMS in the newer antipsychotics. Sharma et
al. (39) report of risperidone-induced NMS in an adolescent male.

There have been no systematic studies of the efficacy of treating delirium in
children or adults with the new atypical antipsychotics. However Sipahimalani and
Masand (40) report of a sixty year old male and a fourteen year old male in whom
delirium was successfully treated with low doses of risperidone. The adolescent
responded to 1 mg of risperidone at bedtime without side effects.

ADJUNCT MEDICATIONS

The antipsychotic medications are considered efficacious in treating delirium
(41). Polypharmacy has been discouraged in children (42). Also, iatrogenic induced
delirium is common. However a few medicines have been used to augment antipsy-
chotics in treating delirium and there may be cases where adjunctive medicine is
deemed appropriate.

population, the use of haloperidol with slow titration to an efficacious dose would seem to be the logical first line approach in treating delirium. If a delirious child with available intravenous access were hospitalized, then intravenous route would be recommended due to the rapid onset of action and the lower incidence of EPS. If the child does not already have intravenous access, clinician judgement would dictate if the severity of symptoms of the delirium require rapid infusion of medicine. The need for EKG monitoring, with intravenous butyrophenone neuroleptic administration in children and adolescents, is questionable. However, we recommend a conservative approach with baseline EKG acquisition followed by cardiac monitoring or daily QTc interval testing. If the QTc interval increases 25% over baseline, then the neuroleptic dose should be discontinued or lowered. The clinical use of droperidol in children is not as well investigated compared to haloperidol. Haloperidol has a longer history of use in the pediatric population, however we consider droperidol an adequate alternative.

There has only been one case report of an atypical antipsychotic (risperidone) used for the treatment of delirium in an adolescent. Atypical antipsychotics have shown efficacy in treating a number of psychiatric conditions in children and adolescents, with minimal short-term side effects. Controlled studies of the atypical antipsychotics in treating delirium are warranted to establish their efficacy.

These recommendations are based on assumptions from adult populations and the limited data available pertaining to children and adolescents. This protocol is not meant for adherence as a protocol proposed from controlled study; rather it is proposed as template for further study and to suffice as other techniques and management are postulated. The lack of data and systematic analysis in the literature pertaining to the treatment of delirium in children and adolescents demonstrates an acute need for structured research in this area.

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