Antipsychotic Treatment Strategies for Delirium in the Pediatric Intensive Care Setting: A Review of the Current Literature

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Interactive References

Background

- There has recently been increased awareness of both the existence and significance of delirium in critically ill children,[1] as well as the challenges to early identification of delirium in this unique patient population, especially in younger patients and those with developmental delays.[2]
- Delirium has been reported in up to 25% of critically ill children.[2]
- Along with multimodal treatment approaches, antipsychotic medications are currently used off-label in the management of pediatric delirium.[3]
- Because delirium is associated with increased hospital length of stay, longer periods of mechanical ventilation, higher costs of care, as well as increased rates of neurodevelopmental regression and mortality,[4] effective prevention and management strategies are crucial for improving these outcomes in pediatric critical care.

Objectives

1. To familiarize the practitioner with antipsychotic treatment strategies for delirium in the pediatric intensive care setting.
2. To review the pharmacokinetics and pharmacodynamics of antipsychotic medications used in the management of delirium in the pediatric intensive care unit (PICU).

Methods

- Current literature about the utility of each antipsychotic was reviewed by conducting a PubMed search of studies from 1964 to March 8, 2023. Articles that were excluded from this review included adult studies, survey-based studies, review or meta-analysis articles, articles published as a case report/case series, letter, or editorial.
- The pharmacokinetics and pharmacodynamics of each antipsychotic were reviewed using the Lexicomp Database.[5]
- Data analysis included descriptive statistics on safety, tolerability, and dosing, as well as data synthesis of the clinical utility of these medications.

Table 1: Evidence and adverse effects of antipsychotics for delirium management in the PICU

Medication + administration route	Dosing range studied	Evidence of studies	Adverse effects noted in studies
Haloperidol PO,[6,7,9] IV,[6,7,9,10] not specified[8]	0.005-0.085mg/kg/day,[6] 0.05-0.15mg/kg/day (divided every 6-12 hr),[7] IQR: 0.025-0.07mg/kg/day,[8] single dose: 0.013-0.278mg/kg,[9] 0.05-0.5mg/kg/day[10]	No statistically significant benefit[6,7,8]	Sedation,[6] cogwheel rigidity,[6] tremor,[6] dystonia,[6,8-10] hyperpyrexia,[9] no significant adverse effects[7]
Quetiapine PO[7,8,11-13]	25-50mg/day (divided every 12 hr)[7] 1.5-6.0mg/kg/day,[8] 0.2-7.0mg/kg/day,[11] 1.5mg/kg/day (divided every 8 hr),[12] IQR (initial dose): 0.5-1.0mg/kg/day + IQR (maximum dose): 0.7-2.0mg/kg/day[13]	Statistically significant decrease in daily doses of opioids + benzodiazepines + PRN requirements of these medications,[12] no statistically significant benefit,[7,13] statistically significant increase in time to final resolution of delirium[8]	QT prolongation,[8,11,13] no significant adverse effects[7,12]
Risperidone PO[7,10,14,15]	0.1-0.4mg/day,[7] 0.2-2.0mg/day,[10] 0.1-0.25mg/day,[14] 0.03-0.08mg/kg/day[15]	No statistically significant benefit[7,14]	QT prolongation,[15] no significant adverse effects[7,10,14]
Olanzapine PO,[16] sublingual,[16] nasogastric or gastrotomy tube[16]	0.625-10mg/day[16]	Statistically significant decrease in the severity of delirium symptoms as measured by the delirium rating scale (DRS)[16]	No significant adverse effects[16]
Chlorpromazine IV[17]	1.6mg/kg/day (divided every 6 hr)[17]	Statistically significant decrease in mean Cornell Assessment of Pediatric Delirium (CAPD) and median State Behavioral Scale (SBS) scores[17]	No significant adverse effects[17]

Table 2: Pharmacokinetics and mechanism of action of antipsychotics for delirium management in the PICU[5]

PO = oral (immediate-release); IM = intramuscular (immediate-release); IV = intravenous (immediate-release); ODT = oral disintegrating tablet

Drug name	Time to peak plasma concentration	Elimination half-life	Bioavailability + other considerations	Mechanism of action
Haloperidol	PO: 2-6 hr IM : 0.3 hr IV: Almost immediate	PO: 14-37 hr IM: 20 hr IV: 14-26 hr	Bioavailability: 60-70% Option of liquid form	Potent D2 antagonist with antagonism of 5HT1 and α-1 receptors
Quetiapine	PO: 0.5-3 hr (pediatric data)	PO: 6 hr (pediatric data)[18]	Bioavailability: 100% (relative to solution)	Potent 5HT2A and D2 antagonist with antagonism of 5HT1A, D1, H1, M1 and α-receptors
Norquetiapine	*2-3 hr (pediatric data)[18]*	*11 hr (pediatric data)[18]*		
Risperidone	PO: 1 hr	PO: 3-20 hr	Bioavailability: 70% Option of ODT and liquid form	Potent 5HT2A antagonist with moderate D2 antagonism and low-moderate antagonism of H1, 5HT1A, 5HT1C, 5HT1D, and α-receptors
9-hydroxyrisperidone	*3-17 hr*	*21-30 hr*		
Olanzapine	PO: 4.7 ± 3.7 hr (pediatric data) IM: 0.25-75 hr	PO/IM: 37.2 ± 5.1 hr (pediatric data)	Bioavailability: 57%[19] Option of ODT	D2 antagonist with antagonism of serotonergic, muscarinic, H1, and α-1 receptors
Chlorpromazine	PO: 1-4 hr[20] IM: 0.25-0.5 hr[20] IV: Almost immediate	PO (Biphasic): Initial 1.1 hr, terminal 7.7 hr (pediatric data)	Bioavailability: 32%	D2 antagonist, with antagonism of H1, M1, and α-receptors

Results

- The twelve studies included 339 pediatric patients who received quetiapine (n=139), haloperidol (n=93), risperidone (n=61), olanzapine (n=32), or chlorpromazine (n=26). A total of 16 (4.7%) of patients were treated with multiple antipsychotics.
- Ultimately, 23 (6.8%) patients experienced adverse effects, with 11 (47.8%) who had dystonia and 9 (39.1%) with QT prolongation.
- One study showed a statistically significant decrease in opioid and benzodiazepine requirements for patients receiving quetiapine, while two other studies demonstrated greater improvement of delirium symptoms, as measured by the DRS, CAPD, and SBS, with olanzapine[16] and chlorpromazine.[17]
- Another study found no short-term improvement in delirium scores for patients treated with haloperidol or quetiapine when compared to untreated patients.[8]
- Despite mixed results and variable dosing strategies, antipsychotic medications appear to play an important role in the management of delirium among pediatric patients within the intensive care setting.

Discussion & Conclusion

- Evidence is currently limited by the lack of randomized, placebo-controlled trials of antipsychotics for delirium in pediatric intensive care unit patients, as well as limited pediatric pharmacokinetic data for antipsychotics.
- Areas for future research include evaluating the long-term effects of short-term antipsychotic use in this patient population, as well as further assessment of the impact of administering antipsychotics on the severity of delirium and requirements for sedative and analgesic medications.
- Given that pediatric delirium has been associated with higher rates of adverse outcomes, including mortality and prolonged length of stay, efforts to improve early prevention, identification, and management of delirium are crucial.

References

1. Schieveld, doi:10.1001/jamapediatrics.2014.125
2. Traube, doi:10.1097/CCM.0000000000002250
3. Capino, doi:10.5863/1551-6776-25.2.81
4. Patel, doi:10.1016/j.pcl.2017.06.009
5. Wolters Kluwer Health, http://online.lexi.com
6. Slooff, doi:10.1097/pcc.0000000000001414
7. Kishk, doi:10.5863/1551-6776-24.3.204
8. Cronin, doi:10.1007/s40272-021-00437-3
9. Ratcliff, doi:10.1097/01.bcr.0000144540.21272.2c
10. Schieveld, doi:10.1007/s00134-007-0637-8
11. Joyce, doi:10.1089/cap.2015.0093
12. Thielen, doi:10.1007/s00246-022-02980-3
13. Caballero, doi:10.1177/10600280231154022
14. Campbell, doi:10.1177/1060028019891969
15. Hutchins, doi:10.5863/1551-6776-26.1.87
16. Sassano-Higgins, doi:10.3233/PIC-13049
17. Kim, doi:10.5863/1551-6776-27.8.725
18. Winter, doi:10.1089/cap.2007.0084
19. Natarajan, doi:10.3109/21691401.2016.1160402
20. Largactil [package insert]. Clinect NZ Pty Limited.

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