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Evaluation of the use of chlorpromazine for agitation in pediatric patients

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Abstract

Introduction: Chlorpromazine is a first-generation antipsychotic used for behavioral problems in pediatric patients. However, other therapies may demonstrate both improved outcomes and fewer side effects. Within our institution, chlorpromazine has been the standard medication used for treatment of pediatric agitation. The study objective was to evaluate the appropriateness of chlorpromazine use (including efficacy, appropriate dosing, drug interactions, and tolerability) to optimize the treatment of pediatric agitation.

Methods: Data regarding drug interactions, patient behavior, dosing, and side effects was collected for each patient administered chlorpromazine from January 2019 through June 2019. Data were analyzed using descriptive statistics assessing the incidence of drug-drug interactions (DDIs), incidences of inefficacy, inappropriate dosing, and side effects.

Results: A total of 70 patients and 130 administrations of oral or intramuscular chlorpromazine were evaluated. Of these administrations, 49 (38%) resulted in a DDI. Eighteen (14%) administrations were ineffective for managing symptoms of agitation. Eleven (8%) administrations were dosed inappropriately, and 46 (35%) administrations resulted in side effects possibly caused by chlorpromazine.

Discussion: Results from this study demonstrate opportunities for improvement in patient care due to instances of drug interactions, inefficacy, inappropriate dosing, and side effects with the use of chlorpromazine.

Keywords: agitation, pediatrics, chlorpromazine, olanzapine, sedation

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Introduction

Chlorpromazine is a first-generation antipsychotic approved for severe behavioral problems in patients 1 to 12 years of age. Chlorpromazine blocks postsynaptic dopaminergic receptors, which accounts for its efficacy as an antipsychotic. Due to its additional effects on the reticular activating system, chlorpromazine can also affect basal metabolism, body temperature regulation, and wakefulness. It can also cause anticholinergic side effects, such as dry mouth or constipation, and alpha-adrenergic side

TABLE 1: Order set dosing (mg) based on age group

Age Range, y	Dosing Options for Agitation[a]	Dosing Options for Severe Agitation[b]
<6	10	12.5
6 to 10	10 OR 25	12.5 OR 25
11 to 17	25 OR 50	25 OR 50

[a]Orally every 6 h as needed.

[b]Intramuscularly every 6 h as needed.

effects, such as hypotension or syncope. Last, as a substrate of CYP2D6, there is potential for several drug-drug interactions (DDIs) with other medications that may increase the concentration of chlorpromazine. This may also increase the risk of QTc prolongation by interacting with other prolonging medications.[1]

Weight-based dosing is recommended for chlorpromazine in children with a dose of 0.55 mg/kg/dose every 4 to 6 hours as needed with a maximum daily dose of 75 mg/d intramuscularly and 500 mg/d orally for patients ≥22.7 kg and ≤45.5 kg. For patients above this weight, a range of 30 to 800 mg/d orally and 200 to 800 mg intramuscularly is recommended.[1]

However, at our institution, preset suggested dosing ranges are utilized within an as-needed order set to facilitate ease of prescribing and administration. Physicians can choose a specific order set based on the patient's age (<6 years, 6 to 10 years, or 11 to 17 years), which contains specific labs and as-needed medications tailored to each age group. For each medication, the physician has the option to select or not select the medication to include it in the admission orders. For each medication, a suggested dose appears based on the average dose for that age group with a drop-down menu to select an alternative dose. Prescribers also have the option to order an as-needed medication separately from the order set. The suggested dosing from the order set is described in Table 1. Although prescribers may individualize therapy at their discretion, using an order set with preset doses based on age may lead to inappropriate dosing.

Additionally, several publications discourage the use of first-generation antipsychotics for agitation in pediatric patients. Deshmukh and colleagues[2] describe the utility of first-generation antipsychotics as limited due to the increased risk of acute dystonia. Another study[3] finds that intramuscular antipsychotics with longer half-lives, such as chlorpromazine, are associated with over-sedation due to the potential depot effect of the route of administration. The most substantial pooled data comes from the Best Practices for Evaluation and Treatment of Agitated Children and Adolescents consensus statement, published in 2019.[4] The authors discourage the use of chlorpromazine in patients with developmental delays due to limited data and also find that second-generation antipsychotics are more widely studied in the pediatric population for agitation. They also describe a study that demonstrates faster resolution of pediatric agitation with olanzapine when compared with lorazepam and chlorpromazine. Overall, several publications and expert consensus panels allude to the preferred use of second-generation over first-generation antipsychotics for pediatric agitation.[4,5]

Due to this growing body of evidence, our institution is considering a change in our pediatric agitation order set. This study aimed to evaluate the appropriateness of chlorpromazine use in regard to its efficacy, appropriate dosing, drug interactions, and side effects as a first step to optimizing the treatment of pediatric agitation.

Methods

This study received IRB approval from Monmouth Medical Center and Rutgers University prior to initiation. A retrospective chart review was performed to evaluate each administration of chlorpromazine used for agitation in a pediatric psychiatric unit from January 1, 2019, through June 30, 2019. Patients that were under the age of 18 and given at least 1 dose of chlorpromazine for agitation were included. Patients were excluded if they did not receive chlorpromazine.

The number of serious DDIs between chlorpromazine and other medications administered to the patients was evaluated using the Lexicomp Interactions tool, which provides risk levels for interactions identified.[6] If the interaction is labeled as risk level D (indicating the need to consider modification of therapy) or X (indicating the drug combination should be avoided) the interaction is labeled as a *serious interaction* within this study.[6]

Efficacy was determined by evaluating notes entered by nursing and support staff within patient profiles after administration. Mental health associates on the unit are required to report on the activity on all psychiatric patients every 15 minutes, and nurses typically document the patient's response within 1 hour of as-needed medication administration. Recorded terms or phrases such as *less agitated*, *relaxed*, or *calm and cooperative* were deemed as effective. Phrases indicating that the patient remained agitated or instances of additional doses or treatments for agitation given within the same day were deemed as ineffective.

Dosing was evaluated by calculating each patient's weight-based dose and comparing it to what was

TABLE 2: Baseline characteristics of the study

Patients, no.	70
Administrations, no.	130
Administrations per patient, mean	1.8
Age, y, mean ± SD	14 ± 2.616
Weight, kg, mean ± SD	64 ± 17.366

administered. The dose was considered inappropriate if it did not fall into the recommended range or exceeded the maximum daily dose. Appropriate dose ranges were based on package insert recommendations.[1]

Any side effects reported after administration of chlorpromazine were evaluated. The Naranjo algorithm was utilized to determine if chlorpromazine was the likely cause of reported side effects.[7] Specifically, the side effect of sedation was defined by staff notes that reported patient was *lying down*, *eyes closed* or *sleeping* within 1 to 2 hours of administration. If the administration took place after 10 PM or other potentially sedating medications were administered, such as diphenhydramine and melatonin, it was determined that alternative causes could have caused the reaction. If the administration took place before 10 PM and no other medications were administered, it was determined that no alternative causes caused the reaction. Temperature irregularities were defined as body temperatures charted as abnormal throughout the inpatient stay (<96.8°F or >98.6°F). Fevers charted before the administration of chlorpromazine were considered an alternative cause of the side effect.

These data were analyzed using descriptive statistics that compared instances of efficacy, potential serious drug interactions, inappropriate dosing, and side effects to the total number of patients and administrations of chlorpromazine. All statistical analyses were performed on Microsoft Excel.

Results

A total of 70 patients and 130 administrations of chlorpromazine were evaluated over the 6-month period. The maximum number of doses administered per patient during the entire inpatient stay was 6 doses and the minimum was 1 dose. Baseline characteristics are further described in Table 2.

A total of 16 (23%) patients' agitation did not respond to chlorpromazine, and 54 (77%) patients showed improvement in symptoms after 1 dose of chlorpromazine. Out of 130 administrations, 112 (86%) were effective, and 18 (14%) were not. A total of 16 (23%) patients experienced a category D DDI, and 8 (11%) patients experienced a category X DDI. Overall, there were 37 (28%) category D and 12 (9%) category X interactions out of 130 administrations. The drug interactions involved were due to either CYP450 2D6 inhibition or risk of QTc prolongation with concomitant use of other prolonging drugs. The medications that interacted with chlorpromazine included olanzapine, ziprasidone, escitalopram (category D interactions), and quetiapine (category X interaction). Within this study, no cardiac-related adverse outcomes or elevated drug concentrations were reported.

Five patients (7%) received doses that were considered inappropriate based on their weight (4 supratherapeutic and 1 subtherapeutic) with 11 (8%) total administrations dosed inappropriately. Ten of these administrations were more than double the recommended dose based on the patient's weight. One dose was approximately half of the recommended weight-based dose. A total of 33 (47%) patients experienced possible side effects due to chlorpromazine (sedation and temperature irregularities) with 46 (35%) instances of side effects possibly caused by each administration of chlorpromazine (Table 3). Side effects occurred in 2 of the 4 patients with supratherapeutic dosing of chlorpromazine with both patients experiencing sedation and 1 patient experiencing temperature irregu-

TABLE 3: Results of chlorpromazine use in pediatric patients

	Occurrences Out of 130 Administrations, n (%)	Patients Out of 70 Patients, n (%)
Risk of category D DDI	37 (28)	16 (23)
Risk of category X DDI	12 (9)	8 (11)
Side effects possibly caused by chlorpromazine[a]	46 (35)	33 (47)
Inappropriately dosed chlorpromazine	11 (8)	5 (7)
Supratherapeutic dose	10 (7.6)	4 (5.7)
Subtherapeutic dose	1 (0.8)	1 (1.4)
No improvement in symptoms after dose of chlorpromazine	18 (14)	16 (23)

DDI = drug-drug interaction.

[a]Side effects included sedation and temperature irregularities.

larities. There were no reports of dry mouth, syncope, hypotension, or arrhythmias.

Discussion

The use of chlorpromazine resulted in several instances of drug inefficacy, interactions, inappropriate dosing, and side effects. The occurrence of these drug interactions can put patients at risk for serious arrhythmias or other toxicities. One study evaluating adults reported an increased relative risk for QTc prolongation with chlorpromazine and considered it a high-risk drug for this adverse effect (relative risk: 1.37; 95% confidence interval = 1.14, 1.64).[8] Additionally, as a substrate of CYP450 2D6, interactions with CYP2D6 inhibitors can lead to a further increased risk of QTc prolongation.[9]

The majority of administrations within this small sample size were effective in managing agitation; however, 13.8% were ineffective. Previous literature alludes to preferred alternatives. In a retrospective study[5] evaluating pediatric patients, chlorpromazine was compared with olanzapine and lorazepam. Intramuscular olanzapine is more likely to produce a calming effect within 30 minutes according to this observational study.[5]

In regard to dosing, the most common dosing error in this study was the administration of supratherapeutic doses to pediatric patients that weighed less than others within their age group. In a cohort study[10] of 28 377 patients, higher doses of antipsychotics were associated with detrimental consequences, including death. Findings in this study, along with other literature, demonstrate the potential for overdosing when preset dosing based on age instead of weight is utilized.

Last, side effects associated with the use of chlorpromazine were most concerning. Out of a total of 46 instances of side effects, 40 administrations (87%) of chlorpromazine resulted in sedation, and 6 administrations (13%) resulted in temperature irregularities. Of these, 8 administrations may have been related to supratherapeutic dosing in 2 patients. Four instances of sedation (10% of the 40 reports of sedation) occurred in 1 patient, and 4 instances of temperature irregularities (67%) occurred in 2 patients who received doses above the recommended weight-based dose. These findings regarding sedation are consistent with previous literature. Within a Cochrane review of 23 trials, sedation was the most commonly reported side effect among adult patients with a relative risk of 2.79 (confidence interval = 2.25, 3.45).[11] Oversedation may go unnoticed when the treatment of agitation is being evaluated. In fact, recommendations from psychiatric treatment guidelines often overlook safety concerns involved with first-generation antipsychotics, such as over-sedation.[12] These findings encourage the use of alternative therapies that have a more tolerable safety profile. Our study found that 40 (31%) out of 130 total administrations resulted in sedation. A similar study[13] evaluating olanzapine for the management of acute agitation in pediatric patients found that only 33 (20%) administrations out of 163 resulted in sedation. These findings imply that, although chlorpromazine is an effective medication for treating agitation, assessing safety and avoiding over-sedation is key to optimizing patient therapy. A future analysis directly comparing outcomes with chlorpromazine and olanzapine in this population is currently being considered at our institution.

This study is limited by its retrospective nature. Additionally, a sample size of 70 patients may not accurately represent the general population. Subjective data were also utilized in the collection of the results. Several data points within this study are based on notes charted by registered nurses and other staff with the assumption that their assessment of the patient is accurate and unbiased. Furthermore, we could not account for missing data, such as vital signs and adverse effects that were not charted. Overall, the nature of a having a small sample size and assessing subjective data led to expected limitations within this study.

Conclusion

This retrospective study demonstrates opportunities for improvement in patient care due to several instances of inefficacy, drug interactions, inappropriate dosing, and side effects with the use of chlorpromazine. Optimization of the use of chlorpromazine for agitation, including incorporating weight-based dosing and EKG monitoring may be potential options in improving pharmacotherapy. The use of alternative therapies, such as second-generation antipsychotics, may also be a potential option to improve patient outcomes.

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