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Safety and effectiveness of intravenous prochlorperazine for intractable vomiting in children with gastroenteritis



Prochlorperazine (PCZ) was first introduced as an anti-psychotic in the 1950s, and subsequently found to be effective to control vomiting. It is a weak dopamine receptor blocker and depresses the chemoreceptor trigger zone (1). Although pediatric studies are limited, research suggests the medication is effective to prevent vomiting, the need for intravenous fluids, and hospital admission. The majority of recent literature has focused on the use of PCZ for the treatment of migraine headaches in young people [2–4]. While PCZ has been noted to be fairly well tolerated by children, it has been found that for some it is only effective as a short-term treatment, some children may not respond to the drug, and there are possibly severe and worrisome side effects such as akathisia and dystonia [1–3]. One study noted that 5% of children treated with PCZ had a definitive diagnosis of akathisia, and 34% presented symptoms suggesting a possible diagnosis of akathisia [1]. Another study on adult patients noted that 16% of patients developed akathisia and 4% developed dystonia, and frequently the onset of these side effects occurred after discharge from the emergency department (ED) [5]. While more definitive trials are needed to discover a more accurate frequency of side effects, treatment with PCZ for migraine or vomiting in children continues. In this study, we will report our results on the effectiveness and tolerability of IV PCZ in consecutive children seen in the ED for a severe, intractable vomiting.

We conducted a retrospective, cohort analysis set in an academic, tertiary-care pediatric emergency department over a one-year study period. All pediatric patients (<18 years) who received IV PCZ for treatment of nausea/vomiting associated with gastroenteritis were included in the study. The diagnosis of gastroenteritis was based on the *International Classification of Diseases, Ninth Revision (ICD-10)* code. The initial dosage of PCZ (0.1–0.2 mg/kg) was chosen at the discretion of the treating physician and infused by slow intravenous injection at a rate not exceeding 2.5 mg/min. Treatment failures were defined as any patient who failed to

respond to PCZ or required an additional anti-emetic within 60 min. Secondary endpoints were akathisia (a strong subjective feeling of restlessness) and dystonia (involuntary muscle spasms or rigidity) documented during the patient’s stay in the ED. To assess accuracy of the data collection, 10% of the records were randomly selected and reexamined by one investigator. The consistency of the recording of data was excellent, with a median kappa statistic of 0.87. Data are reported with 95% confidence intervals (CIs), comparisons were analyzed using chi-square and t-tests.

A total of 390 patients were enrolled, representing 18% of the children who presented to the ED with gastroenteritis during the study period. The mean age was 14.3 ± 2.7 years old (range 2–17). Overall, 202 patients (52%) were initially treated with 0.1 mg/kg PCZ; 188 (48%) received 0.15–0.2 mg/kg PCZ (Table 1). Patients receiving the higher IV dose tended to be older (15.2 vs. 13.5, $P < 0.001$). There were no other differences in demographics, presence of fever, diarrhea, duration of symptoms, or degree of dehydration between the two groups. Overall, IV PCZ acted rapidly and effectively to decrease the intensity of nausea and vomiting in 88% (95% CI 81% to 89%) of the patients at 1 h and 92% (95% CI 88% to 94%) at 3 h. Twenty-four patients (6%) required a second dose of PCZ to control nausea. Thirty-three patients (8%, 95% CI 6% to 12%) required another antiemetic and were considered treatment failures. Fourteen patients experienced akathisia in the ED, one patient subsequently returned to the ED within 24 h with delayed akathisia (4%). One patient had a dystonic reaction in the ED (0.3%). Three patients returned to the ED within 72 h. All had recurrent vomiting and diarrhea requiring rehydration and were able to return home.

Prochlorperazine has been accepted as an effective antiemetic in adults for more than 60 years. This study demonstrates that PCZ is a useful therapeutic approach in the treatment of vomiting in children with gastroenteritis who cannot tolerate oral rehydration. Despite the retrospective design, our data suggests that intravenous dosing results in a relatively small incidence (4–6%) of akathisia and dystonia. A common belief is that the frequency of adverse effects with PCZ is dose related. Our data failed to find a dose related increased frequency of adverse reactions, but these results may have been limited by sample size considerations (Table 1). One patient experienced a delayed reaction to PCZ and returned to the ED with symptoms of akathisia. We also found that akathisia occurred in seven children despite the use of concomitant diphenhydramine. These findings are consistent with other studies evaluating the use of PCZ in children with migraine [2,3]. Emergency clinicians should be aware of the frequency of adverse reactions to PCZ and educate patients and families about the possibility of delayed adverse reactions even after their discharge from the ED [5]. Children with acute illnesses such as gastroenteritis may be more susceptible to neuromuscular reactions, particularly dystonias, than adults [1]. In almost all cases, complete resolution occurred after administration of an antihistamine such as diphenhydramine. Serious adverse effects (e.g., neuroleptic malignant syndrome, seizure, autonomic collapse, tardive dyskinesia) are rarely associated with PCZ use in children [6].

Antiemetics in children with gastroenteritis have not been well studied and their use is somewhat controversial [1]. Recent practices have placed more emphasis on rehydration measures and less emphasis on pharmacologic interventions, however 79% of surveyed emergency medicine physicians reported using antiemetics for children with gastroenteritis in their practice [4]. The most common indications for antiemetic use were to prevent worsening dehydration, avoid hospital admission, patient comfort, and parental concerns [4]. Although PCZ may not be the first choice of treating physicians, it is an effective treatment, although the rate of adverse reactions appears slightly higher than with other

Table 1
Dosing and treatment outcomes for pediatric patients receiving PCZ.

Dose PCZ initially received	# patients	# received concomitant diphenhydramine	Treatment failures	Akathisia/dystonia
0.10 mg/kg	202 (52%)	79 (39%)	22 (11%)	7 (4%)
0.15 mg/kg	89 (23%)	64 (72%)	7 (8%)	3 (3%)
0.20 mg/kg	99 (25%)	89 (90%)	4 (4%)	6 (6%)

antiemetics. Given the frequent use of antiemetics for gastroenteritis in children and adolescents, studies are needed in these age groups to demonstrate safety and efficacy of their use for this condition.

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Public interest in medication-assisted treatment for opioid used disorder in the United States



Opioid-related drug overdose deaths (OD) in the United States (U.S.) continue to increase yearly [1]. Emergency departments (EDs) are the frontline for the overdose epidemic, as well as provide acute treatment for those with opioid withdrawal [2,3]. Evidence-based treatment for Opioid Use Disorder (OUD) exists for managing overdose and withdrawal, as well as for ongoing care with medication-assisted therapy (MAT) [4,5]. Given that emergency physicians are frontline providers in the epidemic, EDs have developed MAT programs for identification, management, and transitions of care [6,7]. However, a paucity of data exists regarding population-level interest in MAT. Internet search queries, as a form of public health ‘surveillance’ and infodemiology [8,9], have previously been used to identify national interest in public health interventions [10–12]. To-date, however, no study has assessed public interest in MAT using this methodology. Therefore, this study sought to assess national interest in MAT and its association with OD across the nation to contextualize the needed expansion of ED-based MAT programs.

We assessed publicly available Google Trends (<https://trends.google.com>) data for the U.S. from January 2004 to December 2018. A preliminary survey of Google Trends was conducted prior to analysis to identify the most frequently searched terms within each category of MAT (drug name; Appendix). If all search terms within each category were positively associated, the most frequently searched term was used for analysis. The final set of terms analyzed included the terms “Naloxone”, “Buprenorphine”, “Buprenorphine/Naloxone”, “Naltrexone”, and “Methadone Clinic”.

Data is reported on Google Trends as a relative search volume (RSV), which is divided by the total searchers in a time range for a selected geographic region (e.g., state), and is then scaled 0 to 100. A value of 100 is peak popularity for the search term. Google discards repeated—i.e., additional—searches by the same person over a short interval of time. At the time of this study, Google's search engine market share among all search engines was approximately 86.9% [13].

The publicly available Multiple Causes of Death from CDC WONDER (<https://wonder.cdc.gov/wonder/help/mcd.html#>) was used to identify crude rate of deaths attributed to opioids between 2004 and 2017, using methods previously described [1].

For the data analysis, RSV of search terms was averaged monthly and yearly at the national level. At the state level, the RSV of search terms were totaled and averaged into a single number generated over the inclusion time period. Crude OD rates were averaged by state and by year. Spearman's rank-order correlation was used to assess the association between RSV and OD. All statistical analyses were run using R (GUI 1.70 El Capitan build). These analyses based on public, aggregate data did not require Institutional Review Board approval.

Between 2004 and 2017, ‘Methadone Clinic’ had the greatest RSV, followed by ‘Buprenorphine/Naloxone’, ‘Buprenorphine’, ‘Naltrexone’, and ‘Naloxone’. Average aggregate RSV per year increased 4.2-fold; from 18.9 in 2004 to 80.8 in 2017 (Fig. 1). Concomitantly, recorded ODs increased from a national average of 10.5 ODs per