Ondansetron for the Management of Vomiting in Children with Gastroenteritis: A Critical Review of the Literature

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Abstract

The purpose of this study was to review the current knowledge on the efficiency, effectiveness, and safety of ondansetron in the treatment of vomiting due to acute gastroenteritis in children. A Medline search using the terms "ondansetron", "vomiting", and/or "gastroenteritis", limited to the pediatric population, yielded only 4 randomized, double-blind controlled clinical trials. Analysis of their primary and secondary outcomes, with calculation of the number needed to treat (NNT), showed that ondansteron is a promising pharmacologic solution for rehydration in this setting, but it harbors a risk of diarrheal complications. Further well-designed prospective studies are warranted to reach a definitive conclusion.

MeSH Words: Ondansetron, gastroenteritis, pediatric, vomiting

A recent paper published in the New England Journal of Medicine, "Oral Ondansetron for gastroenteritis in a pediatric emergency department" [1], suggests that oral ondansetron (Zofran™) reduces vomiting and facilitates oral rehydration in children with acute gastroenteritis(AGE). Although many physicians are familiar with the use of ondansetron to minimize nausea and vomiting due to chemotherapy and during the post-operative period, there is a surprising paucity of literature supporting its use in AGE. A medline search using the terms ondansetron, vomiting, and/or gastroenteritis, limited to the pediatric age group, located only 3 additional clinical studies. The purpose of this article is to review the efficiency, effectiveness, and safety of ondansetron in the treatment of vomiting due to AGE.

Despite the frequency of vomiting as a chief component of many illnesses, its pathophysiology is not well understood. Afferent input from the chemoreceptor trigger zone, vestibular apparatus, cerebral cortex, and GI tract result in the release of multiple neurotransmitters, including dopamine, acetylcholine, serotonin, and histamine [2]. Afferent input arrives at the vomiting center, a nucleus of cells located in the medulla, where efferent impulses are sent to the salivation, and respiratory centers, abdominal muscles, and cranial nerves [2]. The primary site of emetogenesis during the acute administration of chemotherapy may be the gut wall, with serotonin being the primary neurotransmitter [3]. Although the pathophysiology of vomiting in AGE has not been clearly elicited, ondanestron was suggested as a possible adjunctive treatment due to perceived similarities between the two.

An exhaustive review of the pharmacology of ondansetron has been previously published [4]. Ondansetron is a serotonin 5-HT3 receptor antagonist that has been used extensively in children and adults to effectively treat nausea and vomiting due to chemotherapy, radiation therapy, bone marrow transplantation, and post-operative. There is limited data regarding pharmacokinetics in children. Oral bioavailability is about 60% with peak plasma concentrations 1.5 hours after an oral dose. The elimination half-life is 3-3.5 hours. The drug undergoes extensive hepatic metabolization by the cytochrome P450 enzyme system, but surprisingly few drug interactions have been reported.

All 4 of the reviewed studies were placebo-controlled, randomized, and double-blinded. There were no significant methodologic problems that precluded their analysis. The primary outcome used for comparison between these studies was the proportion of children who vomited (yes/no). Secondary outcome measures included the number of episodes of vomiting, the proportion of children requiring IV rehydration, the proportion of children hospitalized, the occurrence of diarrheal symptoms, and the incidence of return visits to ED.

Table 1 is a comparison of the methodologies of the four studies. Although the first study by Cubbeddu is of poorer methodologic quality and consisted of an inpatient population, it was included in this critical review as it was the first study that evaluated the utility of ondansetron in AGE. There is a wide variation in the dose, dosing interval and emesis inclusion criteria; only one used an objective assessment of hydration status. All the studies except that of Reeves used oral rehydration after the administration of an oral dose of ondansetron with IV fluids being administered only to children who were unable to tolerate oral rehydration.

	Age range	Size of study groups (n)	Study setting	Dose and method of administration	Emesis inclusion criteria	Degree of dehydration	Oral vs. IV rehydration	Observation period ED/telephone
Cubbeddu, et al (5) 1997	6mo – 8yr	12 ondansteron 12 metoclopromide 12 controls	Inpatient	Single, 0.3 mg/kg IV	≥2 events in preceding hour	Not assessed	Oral IV rescue	24 h (inpatient)
Ramsook, et al (6) 2002	6mo – 12yr	74 ondansteron 71 control	Outpatient, pediatric ED	1.6 mg-4 mg q8 h for 48 h po	≥ 5 events in preceding 24 h	"Severe dehydration" excluded	Oral IV rescue	Until tolerating oral fluids and voided, 2-3 h/24 & 48 h
Reeves, et al (7) 2002	1mo – 22yr	54 ondansteron 53 control	Outpatient, pediatric ED	Single, 0.15 mg/kg IV	≥ 3 events in preceding 24 h	"Requiring IV hy-dration"	IV only	1 h, maybe more/none
Freedman, et al (4) 2006	6mo – 10yr	108 ondansteron 107 control	Outpatient, pediatric ED	Single, 2-8 mg po	≥1 event in preceding 4 h	Mild to moderate – score assigned	Oral IV rescue	1h/ 3 & 7 d

Table 1. Comparison of characteristics of pediatric studies of ondansteron

	Control group	Treatment group	P value	NNT
Cubbeddu, et al (5) 1997	58%	17%	0.048	2
Ramsook, et al (6) 2002	87%	65%	0.004	4
Reeves, et al (7) 2002	70%	51%	0.04	5
Freedman, et al (4) 2006	37%	14%	<0.001	5

Table 2. Primary outcome measure: incidence of vomiting

	Control group	Treatment group	P value	NNT
Cubbeddu, et al (5) 1997	Not stated	25%	Cannot be calculated	
Ramsook, et al (6) 2002	About 23%	About 13%	0.015	10
Reeves, et al (7) 2002	Not relevant			
Freedman, et al (4) 2006	31%	14%	0.003	6

Table 3. Secondary outcome measure: proportion treated with IV hydration

	Control group	Treatment group	P value	NNT
Cubbeddu, et al (5) 1997	Not applicable- inpatient only			
Ramsook, et al (6) 2002	15%	3%	NS	8
Reeves, et al (7) 2002				
Admitted due to ED protocol	30%	26%	NS	25
Admitted due to hydration failure	23%	7%	0.04	6
Freedman, et al (4) 2006	5%	4%	1.00	10

Table 4. Secondary outcome measure: incidence of hospitalization

Table 2 is a comparison of the studies regarding the primary outcome measure - the incidence of vomiting. All studies demonstrated a statistically significant reduction in vomiting in the treatment group. In order to evaluate the efficiency of this treatment, number needed to treat (NNT) was used as a comparison measure between studies. This is the number of patients that would have to be treated in order to prevent (or achieve) the desired outcome in one patient [5] and is easily calculated when the outcomes in the treatment and control group are known. The NNT, i.e., the number of children who would need to be treated with ondansetron in order to prevent any episode of vomiting, ranged from 2 to 5.

The outcomes for secondary outcome measures are shown in tables 3 and 4. Table 3 demonstrates that the NNT to prevent the need for IV hydration ranged from 6 to 10, although this could be calculated for only 2 studies. As seen in table 4, the significance of the effect of ondansetron on the proportion of children hospitalized varied widely between studies. In the study by Reeves [8], there was no statistically significant difference between the treatment and control groups for those children for whom admission had been predetermined due to ED return or laboratory abnormalities. However, when the remaining pool of 90 children who represented potential ED discharges were analyzed, a statistically significant difference was noted and the NNT becomes similar to that seen in the other two studies.

Although safety was not specifically evaluated in any of these studies, examination of the incidence of side effects was used as a surrogate, albeit ncomplete, measure. The first study of ondansetron for use in AGE by Cubbudu found a 33% incidence of greater than 5 diarrheal stools in the control group as compared to 67% incidence in the ondansetron group; however, there was an 83% incidence in the metaclopromide group, and a much higher incidence of bacterial diarrhea was reported in both treatment groups than in the control group. However, due to these results, diarrhea was considered a possibly significant side effect of treatment and its occurrence was evaluated in subsequent studies as a secondary outcome measure. In the Ramsook study [7], there was no statistically significant difference in the mean number of diarrheal stools during the ED observation period, although there was a statistically significant higher incidence in the treatment group at 24-hour follow-up (1.37 vs. 4.70, p = 0.002); 2 of the 4 ED returns in the ondansetron group were due to persistent diarrhea. The study by Reeves did not find any difference between the groups. The Freedman study found a statistically but not clinically significant difference in the number of diarrheal stools (0.5 vs. 1.4, p < 0.001). Of note, in the Ramsook study 6 doses of ondansetron were administered as compared to 1 dose in the other studies, suggesting that diarrhea may be a dose-dependent side effect. Both the Reeves and Ramsook studies each reported one child in the treatment group who developed a rash. One child in the treatment arm of the Reeves study was

later readmitted with hemolytic-uremic syndrome.

Only 2 of the studies performed follow-up after ED discharge. In the Ramsook study, there was no statistically significant difference in the incidence of emesis (yes/no), or in the mean number of episodes of emesis in the treatment and placebo group at 24 and 48 hour follow-up, but there were significant number of patients lost to follow-up. In the Freedman study, no difference in ED return visits, need for IV rehydration, or hospitalization was found between the treatment and control groups at 3 and 7-day follow-up. However, there was a substantial ED return rate for both groups (19% treatment group, 22% in the control group, p = NS). The Ramsook study also found a higher ED revisit rate as compared to the placebo group (5.41% vs. 0%, p = 0.47).

Ondanestron may be an effective and efficient treatment that reduces the incidence of vomiting in the ED , and is probably a useful adjunct to oral rehydration; however, based on 4 studies it is difficult to firmly advocate its use. A recent Cochrane review, which excluded the Reeves trial due to its incorporation of children over the age of 18, also reached similar conclusions [9]. There is insufficient data to decide if its use decreases the need for IV rehydration in the ED and if it decreases the need for hospitalization. IV administration does not appear to be more effective than oral administration. A multiple dosing regimen has not been shown to be superior to a single dose. The most common side effect, diarrhea, appears to be minimized with a single oral dose. Further studies incorporating more patients need to be performed in order to confirm the results of these studies. In addition, refinement of the primary outcome measure should be considered. One possibility is time to cessation of vomiting as suggested by the authors of the Cochrane review[9]. However, it may not be necessary to have a complete cessation of vomiting in order for ondansestron to be useful in the pediatric ED, but rather to have a decrease in its incidence in order to permit oral hydration and avoid the cost and pain involved with IV hydration. Implementation of an objective protocol for IV hydration coupled with parent teaching would allow success in oral rehydration to be used as a primary outcome measure.

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