CJEM JOURNAL CLUB

Ondansetron for pediatric gastroenteritis

Clinical question

Does ondansetron improve outcome in dehydrated children with gastroenteritis?

Article chosen

Freedman SB, Adler M, Seshadri R, et al. Oral ondansetron for gastroenteritis in a pediatric emergency department. N Engl J Med 2006;20:1698–705.

Study objective

The authors sought to determine whether ondansetron, when given to dehydrated children with acute gastroenteritis (AGE), improves outcome as determined by the presence of vomiting during oral rehydration therapy (ORT), the number of vomiting episodes, and the need for intravenous (IV) rehydration and hospitalization.

Background

Ondansetron is a selective 5-HT3 receptor antagonist primarily indicated for the prevention of nausea and vomiting associated with postoperative states, chemotherapy and radiation therapy in children older than 1 month. Formulations include parenteral and oral solutions, tablets and strawberry-flavoured orally disintegrating tablets.

In 2004, the American Academy of Pediatrics endorsed[1] the Centers for Disease Control and Prevention 2003 guidelines[2] on the management of AGE among children. Although recommendations are not made for routine pharmacologic therapy, the policy states that while often unnecessary, ondansetron may be beneficial in limiting vomiting and hospital admissions. Still, controversy exists regarding antiemetic use in pediatric AGE because of questionable benefit and worry over possible side effects.

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Population studied

Children between 6 months and 10 years of age presenting with AGE to the Children's Memorial Hospital Emergency Department (ED) in Chicago between Jan. 1, 2004, and Apr. 11, 2005, were assessed for study inclusion. Eligibility criteria included at least 1 episode of nonbilious, nonbloody vomiting within 4 hours of triage, at least 1 episode of diarrhea during the illness and mild-to-moderate dehydration.[3] Patients were excluded if they weighed less than 8 kg, were severely dehydrated, had an underlying disease that could affect the assessment of hydration, had undergone previous abdominal surgery, had a hypersensitivity to ondansetron or were previously enrolled in the study.

Study design

The study was a prospective, double-blind, randomized controlled trial (RCT). An enrolment of 214 children was necessary (statistical power of 90%) to detect a 20% reduction in vomiting during ORT, from 35% in the control group to 15% in the ondansetron group (type I error 0.05). Block randomization using groups of 6 and concealed subject allocation was employed. Both the ondansetron (2 mg for children 8–15 kg, 4 mg for 15–30 kg, 8 mg for > 30 kg) and placebo orally disintegrating tablets were similar in appearance and taste and were administered by a bedside nurse. If the patient vomited within 15 minutes, a second

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tablet was given. Fifteen minutes after the administration of the medication, patients were orally rehydrated for 1 hour. Following ORT, the treating physician resumed management. If IV rehydration was ordered, study protocol dictated bolusing 0.9% normal saline at a rate of 20 mL/kg over 30 minutes. Telephone follow-up occurred on days 3 and 7 and a chart audit identified any return visits.

Outcomes measured

The primary outcome was the presence of vomiting during ORT. Secondary outcomes were the number of vomiting episodes during ORT, the number of patients requiring IV rehydration and the number of admissions to the hospital. Vomiting episodes occurring within 2 minutes were recorded as a single episode. Adverse events were identified as such only if there was agreement by at least 2 of the 3 physician investigators acting as safety panel reviewers. They were not identified explicitly prior to the study.

Results

Of 3067 patients diagnosed with AGE during the study period, only 214 met inclusion criteria, could be assessed by the research assistant, had parental consent and were thus randomized to either the ondansetron or placebo group.

In the ondansetron group, 3 of 107 subjects withdrew before treatment and 2 (1.9%) were lost to follow-up. In the control group, all patients received placebo despite 1 not meeting eligibility criteria; 6 of 107 (5.6%) were lost to follow-up.

Of the 104 patients who received ondansetron, 5 vomited within 15 minutes of the first dose but tolerated the second. In the placebo group 3 vomited within 15 minutes of the first dose; however, for 2 of them parental consent was withdrawn before the second dose could be given. The remaining patient tolerated the second dose.

Primary outcome analysis showed a statistical difference in the number of patients vomiting during ORT (15 [14%] ondansetron v. 37 [35%] placebo, $p < 0.001$). After adjustment for the type of physician caring for the child (pediatric emergency physician v. urgent care physician), relative risk (RR) was 0.40 (95% confidence interval [CI] 0.26–0.61).

Secondary analysis revealed that the mean number of vomiting episodes decreased (0.18 for ondansetron v. 0.65 for placebo, $p < 0.001$), with an RR of 0.30 (95% CI 0.18–0.50). Intravenous rehydration was less frequent in the ondansetron group (15 [14%] ondansetron v. 33 [31%] placebo, $p = 0.003$), RR 0.46 (95% CI 0.26–0.79). There was no difference in hospitalization rates (4 [4%] ondansetron v. 5 [5%] placebo, $p = 1.00$).

Adverse event analysis found the ondansetron group had more episodes of diarrhea than the placebo group (1.4 v. 0.5, respectively, $p < 0.001$) and there was 1 case of Kawasaki disease diagnosed 6 days after randomization that was deemed unrelated to ondansetron. Other than 1 episode of urticaria in the placebo group, no other adverse events were considered attributable to either study treatment.

Commentary

The Freedman group asked a useful question and appropriately chose placebo as a comparison, since there is currently no antiemetic recommendation for pediatric gastroenteritis.

The study was well-designed according to the Cochrane[4] and Jadad[5] quality scales. Screening, though, was performed by emergency physicians during night shifts (midnight to 8 am) rather than using dedicated in-house research assistants during the day, which may have introduced selection bias. Also, both pediatric emergency and urgent care physicians were involved in the study. This could be a potential confounder since the decision to admit or start an IV, especially in the context of an unvalidated dehydration scale, depends on training and clinical experience. Analysis, however, showed that there was only a minimal difference and that was adjusted for.

Care was standardized as per the predetermined protocol, except for the experimental intervention. The authors analyzed results as intention-to-treat thus preserving randomization. As per the researchers' successful randomization, reported patient baseline characteristics were similar at the start of the study. There was minimal loss to follow-up in this study, and follow-up data did not affect either primary or secondary outcomes.

Overall, the results showed a statistically significant benefit from ondansetron, compared with placebo, for preventing vomiting during ORT and thus limiting the number of patients requiring IV rehydration. For prevention of vomiting during ORT, the number needed to treat (NNT) was 5 (95% CI 3.2–10.6) and to avoid IV rehydration, the NNT was 6 (95% CI 3.6–17.0). Although these confidence intervals are wide, they still show a benefit of ondansetron treatment even at the modest range of the estimates. One secondary outcome that was analyzed, that is, the rate of hospitalization, did not show any significant difference from placebo. This may be due to a lack of statistical power, since only 9 patients were hospitalized. It may also be that ondansetron does not produce enough beneficial effect to prevent hospitalization in the sicker patients with AGE (e.g., bacterial or human rotavirus).

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The study sample appears to be representative of the pediatric patient population in Canadian EDs. However, less than 10% of patients diagnosed with AGE met eligibility criteria, severely limiting interpretation of the results with respect to the general pediatric population. Applicability may also be questioned since the study used 1 hour of ORT rather than the 4-hour period recommended by the World Health Organization. One can therefore argue that if the children had been given more time for oral rehydration, researchers may not have seen a difference in the need for IV rehydration or an overall difference in vomiting.

Finally, one must consider benefit versus harm when recommending a new treatment. In this study, the main adverse event with ondansetron was a small increase in diarrhea. Although diarrhea can increase dehydration, 1 additional episode is unlikely to be harmful if the patient is then able to tolerate ORT without vomiting. Other known side effects of ondansetron, including sedation and headache, were not measured. Finally, there was 1 case of Kawasaki disease that was not attributed to the treatment by the researchers. If this treatment does become standard practice, it will be important to document any future such cases and other significant adverse events.

As part of the study, a cost–benefit analysis noted that the total expenditure on ondansetron was US$3825 ($35.75/4-mg tablet). Savings were calculated to be $4145 ($124.74/IV catheterization, $1900/admission). This conclusion, however, is incorrect as the authors' calculations included the reduction in 1 hospital admission in the ondansetron group, despite the fact there was no statistically significant difference in admission rates. Nevertheless, an overall cost benefit may still be realized based on a reduced ED length of stay and the availability of generic formulations now available in Canada and the United States.

Of note, the study was partially funded by GlaxoSmithKline, which the authors report had no role other than supplying the tablets.

Conclusion

The study was well-designed and the results appear valid, demonstrating that ondansetron, when given to children in the ED, reduces vomiting as well as decreasing the need for IV rehydration; however, it appeared to increase diarrhea. Although generalizability, applicability and cost-savings must be further analyzed, it is appropriate for EDs to have ondansetron on formulary to offer this treatment option to physicians. Ondansetron use may also help reinforce to clinicians and parents alike that ORT is the treatment of choice in AGE with mild-to-moderate dehydration, despite some initial vomiting. In order to optimize resource use in a busy ED during gastroenteritis season, treatment with ondansetron may help to avoid the need for IV rehydration in children with difficult IV access or resistant parents.

Further research is required to better delineate the pediatric patient population best served by ondansetron use and evaluate the cost implications and adverse effects this change in practice would lead to.

Competing interests: None declared.

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