The Effects of Antiemetics for Children With Vomiting Due to Acute, Moderate Gastroenteritis

ACUTE GASTROENTERITIS (GE) IS A COMMON childhood illness. Although children with GE frequently have vomiting, current practice recommendations for pediatric GE do not include pharmacologic treatment for vomiting. Furthermore, experimental studies of medications to treat pediatric GE-associated vomiting are limited. In this issue of the Archives, DeCamp et al performed a systematic review and meta-analysis to determine if antiemetic treatment reduces vomiting and decreases the need for further intervention in children with GE. Two assessment tools were used to determine the quality rating of each article. The primary outcome measures included cessation of emesis, use of intravenous fluid (IVF) for rehydration, hospital admission, return to care, and medication adverse effects.

Using computerized databases, references lists, and expert recommendations, DeCamp et al identified 11 prospective controlled studies that met inclusion criteria. The 11 articles evaluated 7 different antiemetics, including ondansetron (n=6), domperidone (n=2), trimethobenzamide (n=2), pyrilamine-pentobarbital (n=2), metoclopramide (n=2), dexamethasone (n=1), and promethazine (n=1). The 6 studies evaluating ondansetron, a 5-hydroxytryptamine antagonist commonly used for the treatment of postoperative or chemotherapy-associated nausea and vomiting, included 774 children with a clinical diagnosis of GE. In a meta-analysis, children who received ondansetron treatment were less likely to have ongoing vomiting, be prescribed IVFs, or be admitted to the hospital from the emergency department (ED). However, diarrhea was increased in children receiving ondansetron treatment. The articles evaluating domperidone, trimethobenzamide, pyrilamine-pentobarbital, metoclopramide, dexamethasone, and promethazine had small sample sizes, were of low methodological quality, and produced inconsistent results. Meta-analyses were, therefore, not done to evaluate these antiemetics, nor do DeCamp et al recommend their use. Overall, DeCamp et al conclude that ondansetron treatment is beneficial in moderately ill children with acute GE.

We reviewed this study with regard to the validity of its results, the magnitude and consistency of the treatment effects, and the importance of its findings for clinical practice. We used the framework recommended in Evidence-Based Medicine: How to Practice and Teach EBM to guide our analysis of this systematic review and meta-analysis.

ARE THE RESULTS OF THIS SYSTEMATIC REVIEW VALID?

Is This a Systematic Review of Randomized Trials?

Randomization reduces sources of bias by increasing the chances that the treatment and control groups have similar baseline characteristics and by minimizing the effects of confounders. Including only randomized trials, therefore, increases the validity of the results of a systematic review by reducing bias and random error and by compiling only the highest-level evidence. Inclusion of nonrandomized trials has the potential to magnify the flaws associated with the individual studies and result in less valid results.

This systematic review by DeCamp et al included prospective controlled trials evaluating the use of antiemetic treatment in children with vomiting from GE; they did not limit the review to randomized trials. Although DeCamp et al do not detail the specific inclusion and exclusion criteria for the systematic review, examination of the individual studies reveals that not all of them were randomized. However, the meta-analysis was conducted only on the 6 studies evaluating ondansetron treatment, all of which were randomized, double-blinded, placebo-controlled trials. Accordingly, the ondansetron studies received the highest quality ratings. Thus, the level of evidence springing from the meta-analysis of these 6 studies should be high.

Describe a Comprehensive and Detailed Search for Relevant Trials?

A good systematic review must identify all potential studies that offer evidence related to the research question. Flaws in the process of identifying relevant articles could invalidate the results. An appropriately exhaustive search requires authors of systematic reviews not only to investigate standard bibliographic databases, but also to search journal contents by hand, review bibliographies of related articles, examine relevant conference proceedings, and search for other sources of nonpublished data. A comprehensive, detailed search will limit publication bias; including the results of unpublished studies protects against overestimating the true effect of an intervention if nonsignificant studies were not published. Ex-
aming publications in more than one language should also be considered. This comprehensive search should be described explicitly and transparently in the methods, allowing others to replicate the work if they desire.

DeCamp et al performed an exemplary search for relevant trials. They not only performed detailed searches of the MEDLINE database using PubMed (with search terms described in an appendix available from DeCamp et al), they searched other relevant bibliographic databases, including the Cochrane Collaboration’s Database of Controlled Clinical Trials, the Allied and Complementary Medicine Database (AMED), and the International Pharmaceutical Abstracts database. DeCamp et al hand-scanned reference lists and attempted to locate non-published data using the Clinical Trials Registry and direct contact with experts, but their search for unpublished findings revealed few results. By identifying recent studies that met their inclusion criteria, their search strategies enabled them to locate studies not included in previous systematic reviews on this subject and to draw a very different conclusion about the efficacy of ondansetron treatment.8,9 The difference between the findings of this study and previous systematic reviews highlights the crucial importance of a comprehensive search strategy.

Although they limited their search to English-language studies, this was an appropriate decision based on the failure of the prior Cochrane review to locate any relevant non-English studies. DeCamp et al used 2 statistical techniques to assess publication bias or other reporting biases, although these techniques have only limited power to detect bias.8,9 One possible criticism of the search done by DeCamp et al is that they should have considered repeating their search strategy in the EMBASE database. Prior systematic reviews and comparison searches reveal that the same search strategy in the EMBASE database locates studies not identified by using the same search strategy in MEDLINE (and vice versa).10-12 Another concern is that all the studies included were sponsored by a pharmaceutical company that manufactures ondansetron; this appears, however, to be a result of a lack of non–industry-sponsored evaluations rather than a deficiency of the search strategies.

Were the Individual Studies Assessed for Validity?

Once again, the results of a systematic review are only as valid as the studies it includes. All potential studies need to be considered, and the authors need to assess the validity of individual studies using specific criteria. Individual studies must be assessed for high methodologic quality, and this assessment process must be reproducible. We previously discussed the importance of including high-quality studies, such as randomized controlled trials, to reduce bias. Because the authors’ judgments come into play when making decisions about the validity and which studies to include, using standardized forms to assess individual studies and having multiple authors independently assess the studies increase confidence in the results of a systematic review.

Once again, DeCamp et al used exemplary methods to assess the individual studies in this regard. First, they masked study identifiers to blind those doing the assessments and prevent bias related to knowledge of study authors or institutions. Second, they used not just one but 2 standardized checklists to assess the methodologic quality of the individual studies. Using both the Downs and Black checklist13 and the Delphi process14 increased the reliability of their assessments and allowed for comparison between the scoring systems. Finally, by having 2 independent people participate in the assessment process, DeCamp et al better guarded against errors in the assessment process because any variance in scoring of the studies required discussion and consensus.

Were Individual Patient Data Used in the Analysis?

Using individual patient data from each of the studies, rather than aggregate data, summary tables, or only the published results, allows for the most reliable analyses.4 In particular, if the meta-analysis aims to compare various patient subgroups, using individual patient data may be vital.

While DeCamp et al primarily relied on published data from the individual studies, they did construct 2×2 tables from these data. They also contacted all study authors for data related to their methods, and the investigators provided individual patient data necessary to complete appropriate 2×2 tables for studies where the published results were not sufficient. While DeCamp et al investigated multiple outcomes, including further emesis, failed oral rehydration therapy, and hospital admission, they did not conduct patient subgroup analyses. They used combined data for their random-effects meta-analysis model, a decision justified by the homogeneity of the studies. Thus, although they used primarily aggregate data for these analyses, these decisions were reasonable in light of the analyses conducted and the tests for heterogeneity and publication bias.

ARE THE VALID RESULTS OF THIS SYSTEMATIC REVIEW OF THERAPY IMPORTANT?

Are the Results Consistent Across Studies?

When reviewing the consistency of study results, the number of studies included for each medication should be considered. Little can be said about any of the drugs included other than ondansetron, as a maximum of 2 studies were included for each of the other medications. In addition, these studies were generally older and of lower quality. Given the quality and quantity of these studies, the safety concerns, and limited approval for these antiemetics, DeCamp et al appropriately conclude that none of these drugs should be used as antiemetics for children.

The relative risk (RR) describes the risk of an event relative to an exposure. When comparing a treatment group with a control group, an RR of less than 1 means that the outcome of interest is less likely to occur in the treatment group than in the control group. Within the systematic review, the results of interest for each study are the RRs for the outcomes of hospital admission, receiving IVF, persistent emesis, and returning to ED care. First, we compare the range of the results among the stud-
ies. Then, we look at the pooled estimate when the results of all the studies in the systematic review are combined.

For ondansetron, 5 of the 6 studies evaluated hospital admission as an outcome. The results of these studies were qualitatively similar, with all suggesting decreased hospitalization after ondansetron treatment. However, prior to pooling of the results, the point estimates for the RR show a substantial spread, ranging from 0.17 to 0.86. With all 5 studies taking place in an ED setting and including participants in similar age ranges, the variability cannot be explained by obvious differences in participants. While the confidence intervals (CIs) for the studies overlap fairly well, 3 of the 5 studies have a CI for the RR that crosses 1. The pooled estimate for the reduction of risk of hospital admission is 0.52, with a fairly wide 95% CI of 0.27 to 0.95. When DeCamp et al pooled the results from these studies, they appropriately evaluated the heterogeneity between studies using a Q statistic. We are told that the heterogeneity was not statistically significant, though the P value is not reported. With the point estimates for RR for hospital admission showing a substantial spread, the inclusion of the Q statistic result would have been valuable.

Four of the ondansetron studies investigated whether ondansetron treatment decreased the risk of receiving IVF. The point estimates of the studies are very similar, ranging from 0.36 to 0.50. The CIs for the RRs in these studies almost completely overlap, with the exception of the small inpatient study by Cubeddu et al,13 which has a very wide CI. Pooling of these studies is acceptable, and the pooled point estimate for decreased risk of receiving IVF during ondansetron treatment (0.41) is useful.

Five of the ondansetron studies assessed decreased risk of persistent emesis in the ED as an outcome. For this outcome, the point estimates for RR were again similar (0.38-0.60), with a pooled estimate of 0.45. The good overlap of the CIs for the RR of the individual studies again supports the validity of the results. Among these 5 studies, the study by Reeves et al16 was the one study in this group that had the highest point estimate for RR (0.60), meaning the smallest reduction in risk. This study also had the highest point estimate when looking at hospital admission as an outcome (RR, 0.86). The inclusion of a wider age range of subjects (1 month-22 years) in this study may explain these results.

Five of the ondansetron studies looked at return to care during study follow-up as an outcome. The RR for returning to care did not differ between those receiving ondansetron and those receiving placebo. The indications for return to care were not evaluated, and DeCamp et al could only hypothesize why the treatment and control groups had similar rates of returning to care. Their explanation that more severe cases of GE cannot be treated with only 1 dose of ondansetron is reasonable.

What is the Magnitude of the Treatment Effect and How Precise Is It?

The number needed to treat (NNT) indicates the number of children who would need treatment with ondansetron to avoid a particular outcome. Based on pooled estimates in the meta-analysis of ondansetron studies, the NNTs were low for all 3 of the major outcomes, avoiding hospital admission, avoiding IVF administration, and stopping further emesis. The NNT for hospital admission was 14 (95% CI, 9-44), the NNT to avoid 1 IVF administration was 5 (95% CI, 4-8), and the NNT to stop 1 child from further emesis in the ED was 5 (95% CI, 4-7). The low NNTs to avoid these negative outcomes strongly favor the use of ondansetron treatment for children with vomiting from acute GE. A potential point of critique is that, despite careful quality assessment of the studies using 2 different tools, these calculations were done without using the result of the assessments or weighing the data based on the quality of the studies. The CIs for the NNT to avoid IVF administration and the NNT to stop further emesis were both narrow, suggesting a precise estimate of the treatment effect. The CI for the NNT for hospital admission, however, was wider and not as precise.

CAN WE APPLY THIS VALID, IMPORTANT EVIDENCE ABOUT THERAPY IN CARING FOR OUR PATIENT?

Is Our Patient so Different From Those in the Study That Its Result Cannot Apply?

This meta-analysis primarily includes studies performed in the ED. For ED physicians caring for children, the results of this analysis are very applicable. The results cannot be applied reliably to clinicians in other settings and those caring for children with milder disease.

Is the Treatment Feasible in Our Setting?

Studies evaluating both oral and intravenous administration of medication were included in the analysis. Both are feasible treatment options in EDs in the United States. In addition, the costs associated with ondansetron treatment are not prohibitive, particularly when using an oral formulation.

What Are Our Patient’s Potential Benefits and Harms From the Therapy? Were All Clinically Important Outcomes Considered?

Diarrhea was a documented adverse effect reported in 5 of the ondansetron studies. DeCamp et al conclude that the studies vary widely in regard to duration of symptoms, as well as length of follow-up. Therefore, the data could not be pooled to investigate this adverse effect further. Further evaluations of the adverse effects of ondansetron treatment, particularly in increasing diarrhea, are needed. Other adverse effects were not discussed. Because acute GE is such a common condition in children, ondansetron may become a frequently used treatment in US EDs. In the setting of widespread use, even very rare adverse effects of ondansetron treatment may be important and will require further study.

Vomiting related to GE may be a source of psychological and physical distress for parents and children,17 with some parents linking vomiting with more severe ill-
ness.\textsuperscript{18} In addition, persistent vomiting can lead to dehydration that requires even more distressing procedures, including needle sticks for IV placement or laboratory assessments and hospitalization.\textsuperscript{19} Patients and their families may well expect a cessation of vomiting from the medical therapy they receive when they seek care, and this meta-analysis suggests that ondansetron treatment could meet that expectation, in addition to providing other valued outcomes. Although an increase in diarrhea may not be appreciated, diarrhea may be less distressing to families than persistent vomiting.\textsuperscript{18} At a minimum, parents should be informed about this potential adverse reaction when discussing treatment with ondansetron.

**CONCLUSIONS**

The systematic review published by DeCamp et al suggests that ondansetron is an effective treatment for reducing hospitalization, IVF use, and further emesis for children with vomiting due to acute GE. By using excellent systematic review methods, DeCamp et al present results that appear reliable and valid. The results are consistent across studies of ondansetron treatment, with low NNTs supporting the efficacy of ondansetron therapy. Two previous systematic reviews on this same topic drew a different conclusion and did not support the use of ondansetron treatment for GE-related vomiting.\textsuperscript{9,10} However, this study by DeCamp et al includes more recent studies, and meta-analysis of the new evidence supports their conclusions favoring ondansetron use. Their systematic review also confirms the lack of evidence to support the use of other antiemetic medications, including domperidone, trimethobenzamide, pyrilamine-pentobarbital, metoclopramide, dexamethasone, and promethazine.

For clinicians in ED settings, a strong level of evidence supports the use of ondansetron to prevent hospitalization, failure of oral rehydration therapy requiring IVF, and recurrent emesis in children with vomiting due to moderate GE. There is not sufficient evidence to recommend the use of ondansetron for pediatric GE in outpatient settings or among children with mild disease.

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**REFERENCES**