

Oral Ondansetron to Reduce Intravenous Fluid Rehydration: Context Matters



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As recently as the 1980s, diarrheal illnesses claimed the lives of greater than 4.6 million children younger than 5 years every year.¹ With the development and widespread use of effective treatments, pediatric deaths from diarrheal illnesses have decreased by nearly 90%.² However, diarrheal illnesses still claim the lives of nearly 500,000 children each year, most of which occur in low- and middle-income countries, reflecting the interplay of environmental factors, sanitation, water, food, and poverty.^{3,4} The mainstay of therapy for most cases of pediatric diarrhea in low- and middle-income countries is oral rehydration therapy, continued feeding, and zinc supplementation.⁵⁻⁸ If both these treatment options and preventive measures were routinely available to children across the globe, many childhood deaths from diarrhea could be avoided.⁹

Freedman et al¹⁰ explored the use of the antiemetic ondansetron in children with vomiting and diarrheal illnesses in Pakistan, a country classified as lower-middle income.¹¹ The study team investigated whether a single dose of oral ondansetron administered to children younger than 5 years and with diarrhea but without dehydration reduced rates of intravenous fluid use within 72 hours of presentation to the emergency department (ED). Previous studies conducted in high-income countries have shown that a single dose of oral ondansetron reduces vomiting, intravenous fluid resuscitation, and inpatient hospitalization for children with diarrheal illnesses.^{12,13} However, evidence evaluating the use of oral ondansetron in children with vomiting accompanying diarrheal illness in low- and middle-income countries is limited.¹⁴⁻¹⁶

Freedman et al¹⁰ conducted a double-blind, placebo-controlled, randomized trial in 2 EDs in Karachi, Pakistan. Research in low- and middle-income countries can often be challenging because of lack of research infrastructure.

Nevertheless, in recent years, in response to increased recognition that the world's disease burden lies in low- and middle-income countries, the number of clinical trials conducted in these settings has increased.¹⁷ This increase may also be the result of increasingly complex regulations and high costs of conducting clinical trials in high-income countries,^{18,19} and of recognition of growing markets for pharmaceuticals in low- and middle-income countries.²⁰ However, many have raised ethical concerns about trials in low- and middle-income countries, questioning whether there will be ongoing access to therapies at the conclusion of the study.²¹⁻²³ Although not specifically approved for gastroenteritis in children,^{24,25} ondansetron, a commonly prescribed²⁶ antiemetic medication, may not be widely available in all low- and middle-income countries.

Pediatric clinical trial activity is poorly correlated with pediatric global disease burden,²⁷ and many pediatric trials are discontinued and unpublished,²⁸ with the most pronounced gaps in lower-income countries.²⁹ As such, we applaud Freedman et al for conducting a trial of oral ondansetron in Pakistan, where diarrheal illnesses in children are common, and for insuring publication of the trial's results, even if oral ondansetron had no effect on the administration of intravenous fluids.

The reasons that oral ondansetron did not reduce rates of intravenous fluid are likely multifactorial. First, selecting children without dehydration and relatively fewer episodes of vomiting may account for the lack of effect that other studies have demonstrated in children with mild to moderate dehydration. Second, almost one fifth of children enrolled in the placebo group received antiemetics (eg, dimenhydrinate, domperidone, metoclopramide) either before or after randomization, potentially diluting the effect of oral ondansetron. Furthermore, 16.6% of the placebo group and 13.8% of the intervention group received ondansetron before randomization. Third, the cause of diarrheal illnesses in low- and middle-income countries in comparison to high-income countries, where many of the previous trials of oral ondansetron were conducted, may

differ.^{12,13} In contrast to high-income countries, where viral gastroenteritis is the most common cause of childhood diarrhea,³⁰ pathogenic bacteria and parasites are the most common causes of pediatric diarrhea in many low- and middle-income countries.³¹⁻³³ The efficacy of oral ondansetron may differ by the infectious cause, a hypothesis that needs further investigation. Although only 5% of enrolled patients had stool testing conducted during the trial, these samples may provide additional insights.

Freedman et al¹⁰ have completed the largest trial published to date of oral ondansetron in children with diarrheal illness and without dehydration in a low- and middle-income country. Because the study did not demonstrate a reduction in need for subsequent intravenous rehydration, ED providers in resource-limited settings should not prescribe ondansetron (or likely other antiemetics) to children with diarrheal illness but without dehydration because the potential adverse effects may outweigh any potential therapeutic benefit. Further study is needed to elucidate whether oral ondansetron may reduce rates of intravenous fluid administration in children with dehydration in low- and middle-income countries. Ultimately, clinicians should carefully consider the child's illness severity, the clinical history, and the environment when prescribing oral ondansetron for children with vomiting accompanying diarrheal illness.

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By
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