

Managing paediatric gastroenteritis in primary care:

is there a role for ondansetron?

Despite the reduction in hospital admissions¹ and deaths² due to the rotavirus vaccine, acute gastroenteritis remains a major cause of morbidity and healthcare service use worldwide. While typically a self-limited illness, the mainstay of therapy is oral rehydration therapy (ORT) to prevent the need for intravenous fluids and hospital admission due to severe dehydration.³ In 2006, a randomised controlled trial (RCT) by Freedman *et al* showed that a single dose of ondansetron in the emergency department (ED), compared with placebo, reduces the likelihood of vomiting and the need for intravenous rehydration.⁴ This seminal trial changed the standard of ED care for children with gastroenteritis but evidence was lacking for its use in primary care.

LATEST RESEARCH ON ONDANSETRON IN THE BJGP

In this issue of the *BJGP*, Bonvanie *et al* report an important pragmatic RCT evaluating the addition of oral ondansetron to usual care in children presenting with acute gastroenteritis in the out-of-hours primary care setting.⁵ The trial was conducted between 2015 and 2018 in three Dutch centres for out-of-hours care, and included children aged between 6 months and 6 years diagnosed with acute gastroenteritis — defined as ≥ 4 episodes of vomiting in the 24 hours before presenting, including one episode within 4 hours of presentation.

Usual care for children included the provision of ORT, either 10 ml/kg or 15 ml/kg for 4 hours based on hydration status along with administration instructions. Children randomised to the intervention group received a single dose of oral ondansetron syrup (0.1 mg/kg). The trial was open label without a placebo arm — participants, parents, GPs, and the research team were not blinded. The primary outcome was the proportion of children who continued vomiting in the first

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4 hours after randomisation, while secondary outcomes included number of vomiting episodes in the first 4 hours, ORT intake, adverse events, specialist referrals, hospital admissions, and parental satisfaction.

Of the 1061 participants screened, 437 were eligible, of which 194 children were enrolled, 97 to each arm. The median age of children was 1.5 years, with a median duration of vomiting of 2 days with 71% reporting diarrhoea; the severity of illness was similar between groups. Children who received ondansetron had a 60% [95% confidence interval (CI) = 45% to 81%] reduction in vomiting within 4 hours (42.9% versus 19.5%; number needed to treat = 4), including a reduction in the number of vomiting episodes (incidence rate ratio 0.51, 95% CI = 0.29 to 0.88). However, there was no difference in referral rates (19.2% versus 19.7%) or hospital admission rates (13.7% versus 15.3%) between groups. Median intake of ORT in both groups was only 10 ml within 4 hours while 6.6% reported serious adverse events (such as seizures), with no differences between groups. Parental satisfaction, reported using a 5-point Likert scale, was higher in the ondansetron arm ($P=0.027$).

STRENGTHS AND LIMITATIONS

Bonvanie *et al*’s trial has several strengths. First, it is an excellent example of community GPs working together to address an important clinical area in paediatrics. Nearly 600 GPs collaborated over the trial period, which is a testament to the importance of the topic and

the nimble trial design. Second, despite the open-label design, baseline characteristics of both groups were similar. Third, the authors conducted a parallel controlled cohort study to look at those children who were not enrolled, and highlighted the ethical and logistical challenges in conducting a trial in children in primary care.⁶

However, there are important methodological limitations. First, unlike the original trial by Freedman *et al*, there was no placebo arm. Second, outcome assessors were not blinded: outcomes were ascertained by parent report, which would have directly influenced several outcomes (for example, parental satisfaction). Third, unlike the earlier studies that used a fast-tab ondansetron formulation, Bonvanie *et al* used an oral syrup formulation, which may have a longer onset of action. Fourth, the trial did not meet the expected sample size of 100 patients in each arm. Finally, the outcome was changed from referral to vomiting because of slow recruitment, which is unfortunate as referral would have been the stronger outcome.

COST-EFFECTIVENESS

A linked analysis by Weghorst *et al* in the present issue describes a cost-effectiveness analysis of the trial.⁷ Based on the primary outcome of vomiting within 4 hours, the incremental mean cost for an additional child free from vomiting in the first 4 hours was €9 (95% CI = -€41 to €3), but the CI includes potential increased costs. The difference in cost was driven by the indirect costs of maternal work absenteeism (€35.5/day), which was €287 in the usual care group and €151 in the ondansetron group. Yet, it is not clear how a reduction in vomiting within 4 hours could lead to a 4-day mean difference in maternal days of work missed. Lastly, the comparison excluded the cost of ondansetron (€0.25 to €0.37) yet included the cost of ORT (€0.18 per 25 ml). While the cost may be marginal, all costs should be considered in a cost-effectiveness analysis.

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REALITIES OF PAEDIATRIC RESEARCH

The trial by Bonvanie *et al* highlights the inherent challenges of paediatric trials and why the evidence base in children lags behind that of adults.⁸ In the pilot trial, the medical ethics committee initially required that both parents sign consent for enrolment, consistent with Dutch national regulations. However, only 39% of visits had both parents, which would have made the trial not feasible, which was later modified to immediate written consent by one parent plus immediate verbal consent from the other, followed by written consent by the second parent at a later stage.⁶ Such an onerous ethical burden on families is an unreasonable impediment to including children in trials.⁹ The trial clearly shows the benefit of conducting a pilot study prior to full study enrolment, and importance of tracking patients who do not consent.

WHAT ARE THE IMPLICATIONS FOR THE MANAGEMENT OF ACUTE GASTROENTERITIS IN PRIMARY CARE?

Based on methodological limitations, we are cautious to recommend the adoption of ondansetron into routine care. While this pragmatic trial showed a reduction in vomiting within 4 hours, it had no impact on the amount of ORT provided, specialist referral, or hospital admission. There may be an important role for shared decision making with families that ondansetron may help in the short term by reducing vomiting, but we do not know whether it changes the natural history of the illness or avoids serious adverse events such as hospital admission. Future trials on ondansetron use in primary care should prioritise important clinical outcomes, such as hospital admission or amount of ORT provided.

This study highlights the need for greater emphasis on parental ORT education. In both groups, children were given a median of 10 ml of fluid over a 4-hour period. Based on the median weight of 11 kg, children should have received a minimum of 110 ml (10 ml/kg) or 165 ml (15 ml/kg). The main utility of ondansetron is to reduce vomiting to allow the provision of oral fluid — there is questionable benefit if this does not occur. Newer evidence from the ED setting supports the use of alternatives to oral rehydration solutions, such as diluted apple juice, which

may be more palatable for young children.¹⁰

Future research should focus on two main avenues: 1) testing different solutions for ORT in primary care settings; and 2) developing ORT implementation strategies for those found to be optimal, which may or may not include pharmacological treatments. Clearly, more effort is needed on educating parents (and healthcare practitioners) on the provision of fluids and could successfully use newer communication tools (for example, whiteboard animation videos and animated graphics with narration).¹¹ As is often the case in medicine, the search for a simple drug intervention highlights the critical role of non-drug interventions.

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Provenance

Commissioned; not externally peer reviewed.

Competing interests

Peter J Gill has received grant funding from the Canadian Paediatric Society, Physician Services Incorporated (PSI), and the Canadian Institutes of Health Research (CIHR) in the past 5 years. He is on the editorial board of BMJ Evidence Based Medicine and on the Institute Advisory Board for the CIHR Institute of Human Development, Child and Youth Health, where he has expenses reimbursed to attend meetings. He is a member of the EBMLive steering committee, and he has expenses reimbursed to attend the conference. The remaining authors have declared no competing interests.

DOI: <https://doi.org/10.3399/bjgp21X717089>

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REFERENCES

1. Aliabadi N, Antoni S, Mwenda JM, *et al*. Global impact of rotavirus vaccine introduction on rotavirus hospitalisations among children under 5 years of age, 2008–16: findings from the Global Rotavirus Surveillance Network. *Lancet Glob Health* 2019; **7(7)**: e893–e903.
2. Troeger C, Khalil IA, Rao PC, *et al*. Rotavirus vaccination and the global burden of rotavirus diarrhoea among children younger than 5 years. *JAMA Pediatr* 2018; **172(10)**: 958–965.
3. Freedman SB, Pasichnyk D, Black KJL, *et al*. Gastroenteritis therapies in developed countries: systematic review and meta-analysis. *PLoS One* 2015; **10(6)**: e0128754.
4. Freedman SB, Adler M, Seshadri R, Powell EC. Oral ondansetron for gastroenteritis in a pediatric emergency department. *N Engl J Med* 2006; **354(16)**: 1698–1705.
5. Bonvanie IJ, Weghorst AA, Holtman GA, *et al*. Oral ondansetron for paediatric gastroenteritis in primary care: a randomised controlled trial. *Br J Gen Pract* 2021; DOI: <https://doi.org/10.3399/bjgp2021.0211>.
6. Weghorst AA, Holtman GA, Wolters PI, *et al*. Recommendations for clinical research in children presenting to primary care out-of-hours services: a randomised controlled trial with parallel cohort study. *BJGP Open* 2021; DOI: <https://doi.org/10.3399/bjgpopen20X101154>.
7. Weghorst AA, Holtman GA, Bonvanie IJ, *et al*. Cost-effectiveness of oral ondansetron for children with acute gastroenteritis in primary care: a randomised controlled trial. *Br J Gen Pract* 2021; DOI: <https://doi.org/10.3399/bjgp2020.1093>.
8. Groff ML, Offringa M, Emdin A, *et al*. Publication trends of pediatric and adult randomized controlled trials in general medical journals, 2005–2018: a citation analysis. *Children (Basel)* 2020; **7(12)**: 293.
9. Schot MJC, Broekhuizen BDL, Cals JWL. [Rules and regulations threaten non-pharmacological studies in children]. [Article in Dutch]. *Ned Tijdschr Geneesk* 2015; **160**: A9354.
10. Freedman SB, Willan AR, Boutis K, Schuh S. Effect of dilute apple juice and preferred fluids vs electrolyte maintenance solution on treatment failure among children with mild gastroenteritis: a randomized clinical trial. *JAMA* 2016; **315(18)**: 1966–1974.
11. Albrecht L, Scott SD, Hartling L. Evaluating a knowledge translation tool for parents about pediatric acute gastroenteritis: a pilot randomized trial. *Pilot Feasibility Stud* 2018; **4**: 131.