Critical Review Form
Therapy

Randomized Controlled Trial Comparing Oral Ondansetron with Placebo in Children Vomiting from Acute Gastroenteritis, *Annals EM* 2002; 39: 397-403

Objective: To assess whether oral ondansetron to patients (age 6 months to 12 years) leads to clinically relevant reduction in vomiting and rates of IVF administration (p.399)

Methods: RCT at Baylor Children's Hospital with inclusion criteria of >5 episodes of vomiting in the preceding 24-hours without antecedent anti-emetic use. All parties were blinded (ED staff, investigators, pharmacy, outcome assessors, and patients' families) to treatment arm. Exclusion criteria included chronic underlying condition, possible appendicitis, suspected UT1, or (undefined) "severe" gastroenteritis. Placebo was color and taste matched equivalent with dosing based upon Oncology literature, oral re-hydration commenced 15-minutes after treatment with either Pedialyte or Pedialyte/Gatorade mix as per ED protocol. Follow-up occurred by phone and mailed diary. Primary outcome was the frequency of emesis in the 48º after ED evaluation and the ED rates of IVF administration. Secondary outcomes were admission rates and frequency of diarrhea. Patients were discharged home with 5 additional ondansetron doses (one every 8º x 2 days) + BRAT diet instructions.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "Using standard random number allocation tables" (p.399)
2.	Was randomization concealed (blinded)?	Yes. "The study was double-blinded in that neither the investigators (including persons administering the drug, ED staff, and outcome assessors) nor the patients and their families knew of the treatment assignment. (p.399)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. The intention-to-treat analysis was followed". (p.400)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Although more boys in Ondansetron group and more severe vomiting in Ondansetron group (Table 1, p.400).
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No, minimizes *adherence* bias.
2.	Were clinicians aware of group allocation?	No, minimizes *co-intervention* bias.
3.	Were outcome assessors aware of group allocation?	No, minimizes *verification* bias.
4.	Was follow-up complete?	No. 18/145 (12%) lost to 48-hour follow up so the authors should have conducted a sensitivity analysis. (Fig 1. p. 401)

II.	What are the results (answer the questions posed below)?	
1.	How large was the treatment effect?	• 145 patients were randomized with emesis frequency after enrollment ranging 0-7 in the placebo group and 0-2 in the treatment group. • Reduction in those with no vomiting during ED stay 87% to 65% although no change in 24- or 48-hour vomiting rates. **NNT 4.5** ($p<0.001$), Table 3, p.400 • No difference in mean or median episodes of vomiting at 24- or 48-hours. • Less patients in Ondansetron group received IVF (23% vs 8%, NNT 6.7) or were admitted (16% vs. 2.5%, NNT 7.4) (Figure 2, p.402). • Zofran group had ↓ ED length-of-stay (2- vs. 3-hours, p = 0.069). • Zofran group had 3 x ↑ diarrheas at 48-hours. • Only 1 macular rash developed in Zofran group, but no other manufactures reported SE noted Sensitivity analysis (not reported in paper) • Assuming all 9 Zofran lost to follow up were either vomiting or not vomiting Δ 24° rates to 50% (Zofran) vs 42% (Placebo) (all Zofran vomiting-- all placebo not) or 62% (Zofran) vs. 52% (placebo) (all Zofran not vomiting, all placebo vomiting). Important to analyze because *study underpowered* and may not have detected a difference at 24º or 48° (Type II error).

2.	How precise was the estimate of the treatment effect?	CI not reported so unable to assess precision of estimates.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes, vomiting children in a busy academic pediatric ED
2.	Were all clinically important outcomes considered?	No. No analysis of patient satisfaction scores, parental lost work/wages, cost-effectiveness, side effect profile.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes, if oral ondansetron can reduce the need for IV insertion while decreasing ED LOS and admission rates and improving symptom relief, no real downside exists.

Limitations

1) **Severe gastroenteritis (whatever that may be) was excluded. More severe patients may have varying treatment effects in favor of or against ondansetron.**
2) **Underpowered (limited by gastroenteritis season!)**
3) **Significant lost to follow up with performing a sensitivity analysis (see above).**
4) **No Confidence Intervals or NNT reported.**
5) **No formal assessment of compliance or adverse drug reactions.**
6) **Industry sponsored with financial incentive for bias.**
7) **No cost-effectiveness analysis.**

Bottom Line

Single-center, industry sponsored well-designed RCT with true multi-level blinding in pediatric (6mo – 12yr) patients presenting to an academic pediatric ED with > 5 episodes vomiting over the preceding 24-hours benefit from oral ondansetron followed by oral re-hydration and BRAT diet protocol with decreased vomiting (NNT 4.5) during the ED evaluation, decreased need for IVF (NNT 6.7) or admission (NNT 7.4). The benefit does not extend to 24- or 48-hours post-ED discharge although the study was not powered to detect this difference. The ondansetron group had three-fold higher risk of diarrhea at 48-hours.