Critical Review Form

Therapy

Oral Ondansetron for Gastroenteritis in a Pediatric ED *NEJM* 2006; 354: 1698-1705

Objectives: **"To determine whether the administration of a single-orally disintegrating ondansetron tablet to children with vomiting and dehydration as a result of gastroenteritis would control vomiting with minimal side-effects." (p.1699)**

Methods: **"Prospective, double-blind, randomized comparison of ondansetron and placebo to control vomiting among children 6 months through 10 years of age" at Children's Memorial Hospital in Chicago. All children with ≥ 1 episode of nonbilious, nonbloody vomiting plus at least 1 episode of diarrhea with mild to moderate dehydration in the preceding 4 hours were approached. Exclusion criteria included weight < 8 kg, severe dehydration, underlying disease compromising assessment of hydration, failure to consent or previous enrollment. A baseline, non-validated dehydration score was recorded prior to randomization in blocks of six by an independent statistician. Ondansetron or similar testing/appearing placebo was delivered in an opaque package by pharmacy and administered by bedside nurse out of the view of the research assistant.**

If vomiting occurred within 15-minutes a second dose was administered. Fifteen minutes after the dose, one-hour of oral rehydration therapy was initiated using a World Health Organization (WHO) oral electrolyte solution (Enfalyte) before the treating physician re-assessed the need for IVF. If IVF were administered, it was at the physician's discretion and per protocol 20cc/kg normal saline.

Follow up occurred via phone at Day 3 and 7. Primary outcome was the proportion of children who vomited while receiving oral therapy. Secondary outcomes were the number of episodes of vomiting during oral treatment, the proportions who received IVF, and hospitalization rates. Adverse events were reported. The study was powered to detect a 20% reduction in the primary outcome at 90% with 2-sided α 0.05 including a 10% non-adherence rate. A mixed-effects linear regression model was used with the physician as the random effect. The advantage of the mixed-effects model are multiple: permits random (as opposed to solely fixed) effects; allows more flexibility in modeling error co-variance; allows error term to exhibit non-constant variance (an assumption of General Linear Modeling); and can handle missing data more efficiently. Overall, the mixed-effects model offers a more robust model and more conclusive research results.

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. "Randomly assigned in blocks of six" (p.1700)
2.	Was randomization concealed (blinded)?	Yes. "To ensure that the research assistant, physician, child and caregiver, __ remained unaware of treatment assignment". The bedside nurse administrated therapy with research assistant out of the room".
3.	Were patients analyzed in the groups to which they were randomized?	Yes, "according to the intention-to-treat principle" (p 1702)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Table 2 (p 1702) displays no major differences in baseline prognostic characteristics.
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. Taste / appearance matched placebo so *adherence bias* (among other confounding effects) minimized.
2.	Were clinicians aware of group allocation?	No. Administered while not in the room so *co-intervention bias* (among other confounding effects) minimized.
3.	Were outcome assessors aware of group allocation?	No so *verification bias* (among other confounding effects) minimized.
4.	Was follow-up complete?	Yes. Figure 1, p.1701 displays excellent follow up at 3 and 7 days (96%).
II.	**What are the results (answer the questions posed below)?**	

<table>
<tr>
<td>1.</td>
<td>How large was the treatment effect?</td>
<td>

243/2624 eligible, 215 consented and randomized.
The interaction between treatment group and whether a child vomited was significant.
Significantly more diarrhea in Zofran group (1.4 episodes versus 0.5, p<0.001).

<table>
<tr><th></th><th>Ondansetron</th><th>Placebo</th><th>NNT</th></tr>
<tr><td>Any post-tx vomiting</td><td>14%*</td><td>35%*</td><td>5 (3.2-10.6)</td></tr>
<tr><td>Mean # episodes vomiting</td><td>0.18*</td><td>0.65</td><td>N/A</td></tr>
<tr><td>Received IVF</td><td>14%</td><td>31%</td><td>6 (3.6-17)</td></tr>
<tr><td>Hospitalized</td><td>4%</td><td>5%</td><td>NS</td></tr>
<tr><td>ED LOS (minutes)</td><td>106</td><td>120</td><td>p = 0.02</td></tr>
</table>
* p < 0.001
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<tr>
<td>2.</td>
<td>How precise was the estimate of the treatment effect?</td>
<td>Narrow CI on RR and NNT which do not cross the line of no effect (one).</td>
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</table>

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, no reason to suggest busy academic pediatric ED in Chicago differs from our busy St. Louis Children's Hospital.
2.	Were all clinically important outcomes considered?	No, investigators did not assess parental satisfaction scores or time to vomiting satisfaction (patient oriented evidence). Remember to distinguish disease oriented evidence (DOE's) from patient oriented evidence that matters (POEM's) while reading the medical literature.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes, oral ondansetron diminishes vomiting episodes while increasing oral intake and decreasing ED length-of-stay with possible cost-savings ($3825 for ondansetron treated group versus $4145 for the placebo group based on IVF & hospitalization costs. However, this was not a cost-effectiveness analysis.

Limitations

1. **Single center study with possible different practice patterns (limited external validity).**
2. **Unvalidated dehydration scale (arguably with face validity).**
3. **Industry sponsored, although GlaxoSmithKline "had no role in the conception, design, or conduct of the study or in the analysis or interpretation of the data" (p 1700) seemingly minimizing *commercial bias*.**
4. **Viral gastroenteritis was diagnosed clinically, although such is reality and likely increases external validity. Carolyn Clancy argues for such real-life diagnostic strategies to maximize applicability of research findings in everyday ED's (Clancy C, et al. Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy, *JAMA* 2003; 290: 1624-1632).**
5. **Did not assess patient-oriented evidence that matters like time to vomiting resolution or parental satisfaction.**

Bottom Line

A single dose of oral ondansetron in children with ≥ 1 vomiting and diarrhea in the preceding 4-hours with clinically suspected gastroenteritis improves the success of oral hydration compared with placebo with NNT 5 (95% CI 3.2-10.6) to prevent post-treatment vomiting in one child. Although rates of diarrhea increase and hospitalization rates are unchanged, a single dose of oral ondansetron in the ED can diminish oral rehydration failures while reducing IV cannulation rates and ED length-of-stay. Future studies should include patient-oriented outcomes.