ACEM: 35th Annual Scientific Meeting

Randomized placebo-controlled trial of droperidol and ondansetron for adult emergency department patients with nausea.

Meek, Mee, Egerton-Warburton, Graudins, Blecher, Pouryaha, Meyer, Fahey, Crow.

- **Monash Health Emergency Medicine**
- **Department of Medicine, Monash University**

MONASH EMERGENCY MonashHealth

MONASH University

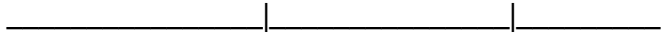
MonashHealth

Why do an ED-based antiemetic RCT?

- **Lots of ED patients have nausea**
- **We frequently prescribe antiemetics**
- **But do they work?**
- **Cochrane Review 2015 conclusion:**
  - ***No convincing evidence for effectiveness of antiemetic drugs over placebo for adult ED patients***

Interlude: ‘Effectiveness’ measurement?

VAS: 100 mm line - patients mark their response. The rating is measured in mm from the left end. An example is shown:



No nausea (40 mm post) (80 mm pre) **Worst nausea imaginable**

Measured VAS change calculation: 40 – 80 = **-40 mm.**

The negative number is a conceptual aid, indicating symptom reduction.

In that case, why another study?

- They may not ‘work’, but the study results are difficult to clinically interpret
- Example: Egerton-Warburton et al, 2014
  - Ondansetron 4mg: mean VAS change -27 mm
  - Placebo: mean VAS change -23 mm
- No statistically significant difference
- Conclusion: Treatments equivalent
- What’s difficult about interpreting that?

Imagine the clinical conversation:

- Patient: (looking up from the vomit bag)
  - Doc, have you got a nausea drug that works?
- You:
  - If I give you nothing, your nausea will improve by 23mm on the VAS. If I give you ondansetron it'll improve by 27mm.
- Patient:
  - Is that good?
- You:
  - Yes, no, maybe. I don't know. Do you want it or not?

Possible solution

- Recent research: VAS change > -8 mm reliably predicts improvement (‘a little’ or ‘a lot’)
- Why?
- Because when symptoms remain ‘the same’, mean VAS change is tightly concentrated around 0 (95% CI: +/- 5 mm)
- This outcome measure uses the definition: efficacy = beneficial effect (symptom improvement)

Additional patient-related solution:

- Other research: 87% of patients expect drugs should make their nausea ‘a lot’ better
- But non-universal agreement means a VAS change cut-off not so reliable for detection
- Best asked through individual direct questioning (Did drugs give the desired effect? Yes or No.)
- This outcome measure uses the definition: efficacy = desired effect (symptoms ‘a lot better’)

Plan:

- Do another placebo-controlled RCT but using a VAS change cut-off level > -8 mm as the primary outcome measure
- Report ‘traditional’ group mean VAS changes as secondary outcomes
- Also ask: Did the treatment have the ‘desired effect’ for you? Yes or No.
- Advantage: From the patient point-of-view, we should know exactly what the results mean

This trial:

- Triple blind RCT, Monash Health EDs
- Ondansetron 8mg versus Droperidol 1.25mg versus Placebo
- Superiority design based on re-analysis of the 2014 paper: suggested ondansetron might improve 79% versus placebo 57%
- Absolute difference about 20% and NNT of 5 would be clinically worthwhile
- N = 111 per group (alpha 0.05, beta 0.9)

Trial under way, but…..

- Ongoing sample size anxiety
- Very limited evidence on symptom improvement rates (one post-hoc analysis)
- Mean VAS change results notoriously variable between past studies
- Examples from different studies
  - Ondansetron -34mm and -22mm
  - Placebo -39mm and -16mm
- Was our sample size estimate anywhere near correct?

Interim analysis (for better or worse)

- Conducted after recruitment 215 patients
- **No possibility of demonstrating superiority**
- Study ceased and reported
- All baseline variables same between study sites and study groups
  - Age 40’s
  - Females 60%
  - Baseline VAS 60mm

Results: 'Traditional'

Mean VAS change — **Individual treatment groups**

Droperidol (n = 73)	Ondansetron (n = 71)	Placebo (n = 71)
-29 mm [-36 to -23]	**-34 mm** [-41 to -28]	**-24 mm** [-29 to -19]

Mean VAS change — **Between-group differences**

Droperidol – Placebo	**Ondansetron – Placebo**	Ondansetron - Droperidol
5 mm [-3 to 13]	**10 mm [2 to 18]**	**5 mm** [-4 to 14]

Primary outcome: Improved or not?

	Individual treatment groups		
	Droperidol (n = 73)	**Ondansetron** (n = 71)	**Placebo** (n = 71)
VAS change ≥ -8 mm: n (%) [95% CI]	55 **(75%)** [64 to 85]	57 **(80%)** [69 to 89]	54 **(76%)** [64 to 85]
	Between-group differences		
	Droperidol – Placebo	**Ondansetron – Placebo**	**Ondansetron - Droperidol**
Difference: % (95% CI) and NNT	**-1%** [-15 to 13] NNT = 99*	**4%** [-10 to 18] NNT = 25	**5%** [-9 to 19] NNT = 20

MONASH EMERGENCY MonashHealth

MONASH University

MonashHealth

Secondary: Desired effect or not?

Experienced desired effect	Individual treatment groups		
	Droperidol (n = 73)	**Ondansetron** (n = 71)	**Placebo** (n = 71)
	56 **(77%)** [65 to 86]	52 **(73%)** [61 to 83]	42 **(59%)** [47 to 71]

Experienced desired effect	Between-group differences		
	Droperidol – Placebo	**Ondansetron – Placebo**	**Droperidol - Ondansetron**
	18% [3 to 33] **NNT = 5**	**14%** [-1 to 29] **NNT = 7**	**4%** [-10 to 18] **NNT = 25**

MONASH EMERGENCY MonashHealth

MONASH University

MonashHealth

Conclusions

- Traditional?
  - One statistically significant difference (Ondansetron vs Placebo) but clinical significance uncertain
- ‘New’ primary outcome
  - 75-80% of patients in all groups are improved to some degree
  - Active drugs **NOT** superior to placebo
- ‘New’ secondary outcome
  - Active drugs **more likely** to give ‘desired treatment effect’ with NNT 5 - 7

So they are worth giving?

- Benefits are fairly debatable, but at least we can now better clinically interpret them and weigh them against the risks

- Risks? Very little:
  - Cost: Droperidol and Ondansetron are cheap
  - Side-effects: 37% mild drowsiness with Droperidol (15% for ondansetron and placebo), nil else

What do we do then?
New conversation:

- Patient: (looking up from the vomit bag)
  - Doc, have you got a nausea drug that works?
- You:
  - 75-80% of people improve whether or not they have a drug, but 1-in-7 feel they improve a bit more if they do have a drug.
- Patient:
  - Is that good?
- You:
  - 1-in-7 is often considered worthwhile. Side-effects are minimal. Do you want it or not?

Future research?

- If the drugs don't do very much, do we need any more ED-based studies? Yes!
- Research to date: one dose of one drug, effect measured at one time, for all conditions
- It may be different with:
  - Different/multiple doses of one drug
  - Combinations of different drug types
  - Condition-specific research (+/- characterize responders versus non-responders)
  - Different outcomes (measures and timing)

The End

- Thankyou
- Questions?

MONASH EMERGENCY MonashHealth

MONASH University

MonashHealth