Author's response to reviews

Title: Erythromycin Lacks Colon Prokinetic Effect in Children with Functional Gastrointestinal Disorders, A Retrospective Study

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Author's response to reviews: see over
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Dear Dr. Marlee

We thank the reviewers for their helpful comments. We have revised the manuscript to address most of the reviewers concerns and have highlighted the responses. Our responses are as follows:

Reviewer #1: Hiroyuki Kuwano

Major revisions

1. There was no Figure in this manuscript. Typical results of manometric recording for colonic examinations, including the effects of erythromycin, bisacodyl, and meal (gastrocolic response) on the recording, should be demonstrated.

We have added a figure showing HAPCs following bisacodyl stimulation. Comparison by visual inspection of a 2 hour recording panel will be difficult. Hence, we have not included the figure showing gastrocolonic response or effect of erythromycin.

2. The results, including the effect of erythromycin on AUC, the patterns of gastrocolic response, and an incidence of HAPC before and after the bisacodyl administration, should be summarized in Tables.

We have added a table to summarize the results of the study.

3. The authors showed that there was no HAPC at the time following the meal. Is this finding to be an abnormal? Is this finding a feature of patients with functional constipation and/or fecal incontinence? There have been some reports that study the colon manometry of pediatric patients with chronic constipation. The author could refer the manometric results of these reports, and discuss or suggest the feature of colonic motility in the patients with chronic constipation.

Normal colon motility in children has two features: 1. gastrocolonic response and 2. Spontaneous or bisacodyl stimulated antegrade propagating HAPCs. These two features are absent in children with organically caused intractable constipation (Please see reference 25). Therefore lack of HAPCs following the meal would not be an abnormal finding if HAPCs were present following bisacodyl stimulation, which was the case in all our patients. We have amended the text to make this point clear (paragraph 1, page 6).

4. The authors should discuss the mechanism of down regulation of erythromycin on the colonic motility. It would be thought that erythromycin
should affect the colonic motility because of significant down regulation after the administration of erythromycin. Please discuss the mechanism of this phenomenon.

We have included a text (paragraph 2, page 8) to mention that reduced expression of the motilin receptor could be one of the reasons for lack of erythromycin response in our subject. The other possible causes were already discussed and changed in the manuscript as suggested by the reviewer.

Minor revision

5. The patients age profile was included in Results. This information would be suitable to be described in Materials and Methods.

We feel that this data would be better presented in the results. However, we are happy to move it to the methods section and will leave the decision with the editors.
Reviewer #2: Menachem Hanani

Major compulsory revisions

1. Colonic mechanical activity was assessed by measuring the area under the curve (AUC), which was calculated by assuming that the response is triangular. However, there is no evidence that this is so. The authors should present several original recordings to confirm this point. I suggest that they measure the actual AUC.

We have reviewed the method of calculating the area under the curve with the software engineer from Medical Measurements System and can confirm that the software used in fact measured the actual area under the pressure line and not the triangular conversion as reported previously. We would like to thank the reviewers for picking this up and have changed the manuscript accordingly.

2. The authors concluded that erythromycin has no prokinetic effects on the colon. They do not address the question whether or not motilin receptors are present in this tissue, although from their discussion it might appear that they expect that this is the case. They should look in the literature for evidence for motilin receptors in the human colon.

Please see paragraph 2, page 3 of the manuscript. We have included references regarding the presence of motilin receptors in the colon.

3. A more serious point is the lack of a control group, i.e. children with no constipation.

We agree with the reviewer that these are not normal children. Previous studies (Reference 25) have reported that patients with a normal gastrocolonic response and antegrade propagating HAPCs during colon motility evaluation do not have an organic disease and are diagnosed with functional constipation. All patients in our study had no identifiable disease to account for their symptoms despite an extensive work up and all were diagnosed with functional constipation. This is probably the nearest to a “healthy control” group we have in a pediatric study to evaluate the effect of erythromycin on colon contractions in children. Moreover it would be extremely difficult to get an IRB approval to perform colon manometry studies in healthy children as the study requires a bowel preparation and a colonoscopy for motility catheter placement before a colon motility study can be performed. We therefore selected patients with chronic constipation who had a normal colon manometry study and were diagnosed with functional constipation after a negative work up.

4. It might be argued that the abnormal motility in the patients is due to reduced expression of motilin receptors, or some other defect in the function of these receptors.
We agree with the reviewer that one of the reasons for lack of erythromycin response could be an alteration in motilin receptor expression. We have included this in the text as one of the possible reasons for lack of erythromycin response in our patients (please see paragraph 2, page 8).

**Minor Essential Revisions**

1. Ref. 4 is not on motilin
   We have amended the text and added a reference to make this clear.

2. The units for the AUC should be mmHg and not mmHg/s.
   We made appropriate changes in the manuscript as suggested by the reviewer.

3. P. 4, patients with normal colonic motility were selected for this study. But these patients suffered from chronic constipation. Please explain
   Please see response to question 3 in major revisions.

4. The authors ignore published work that indicated that erythromycin has no prokinetic influence on humans colon; for example: Jameson JS et al., Oral or intravenous erythromycin has no effect on human distal colonic motility. Aliment Pharmacol Ther.;6:589-595, 1992.
   We have included references as suggested by the reviewer.

4. Style corrections:
   P. 2, "patients with normal (what?).."
   P. 3, "observational studies" (?)
   P. 3, "Data is".
   We have made appropriate changes in the text.

Again, thank you for reconsidering this work for publication in BMC. We hope these changes adequately address the points discussed by the reviewers.

Sincerely,

Narayanan Venkatasubramani