Bustos Fernández, Luis María; Prizont, Robert; Soifer, Luis Oscar
A controlled pilot study on the efficacy of a low dose antibiotic for the treatment of chronic constipation in patients receiving a high fiber diet
Acta Gastroenterológica Latinoamericana, vol. 43, núm. 4, diciembre, 2013, pp. 275-278
Sociedad Argentina de Gastroenterología
Buenos Aires, Argentina

Available in: http://www.redalyc.org/articulo.oa?id=199329343008
A controlled pilot study on the efficacy of a low dose antibiotic for the treatment of chronic constipation in patients receiving a high fiber diet

Luis María Bustos Fernández,1 Robert Prizont,2 Luis Oscar Soifer3

1 Instituto de Gastroenterología “Dr Bustos Fernández”, Ciudad Autónoma de Buenos Aires, Argentina.
2 Medical Consultant on Gastrointestinal Drugs and Pharmaceuticals, Miami Beach, Florida, EE.UU.
3 Servicio de Gastroenterología, CEMIC (Centro de Educación Médica e Investigaciones Clínicas “Norberto Quirno”), Ciudad Autónoma de Buenos Aires, Argentina.

Acta Gastroenterol Latinoam 2013;43:275-278

Summary

Background and aims. In a previous uncontrolled experiment, oral vancomycin improved the symptoms (S) of chronic constipation (CC). The aim of this 21 day controlled pilot study was to determine if a low lincomycin dose improved the S of CC patients unresponsive to a high fiber diet.

Methods. On days 0-to-10, patients were randomized to 500 mg oral lincomycin + high fiber (L+F) or to placebo + high fiber (P+F). Participants and patients were blinded. From days 10-to-21, patients were continued solely on the high fiber diet. The primary efficacy endpoint was the difference in S between L+F and P+F from days 0-to-21 using a visual analog scale (VAS) calibrated from 0=severe S to 10=asymptomatic.

Results. The means of all S were significantly improved by L+F but not by P+F. A significant higher proportion of L+F patients increased the VAS ≥ 3 points.

Conclusions. The initial course of L facilitated the effect of F probably by its effect on the colon flora. This sequence of flora-altering biologics + F may serve as model to replace chronic use of drugs.

Key words. Fibre, antibiotics, lincomycin, chronic constipation.

Resumen

Antecedentes y objetivos. En un estudio previo no controlado, se demostró que el uso de vancomicina oral mejoraba los síntomas de la constipación crónica. El objetivo de este estudio piloto controlado de 21 días de duración fue determinar si la lincomicina a bajas dosis mejora los síntomas de pacientes con constipación crónica refractarios a la dieta rica en fibra.

Métodos. Los pacientes fueron randomizados a recibir 500 mg de lincomicina oral + fibra dietética (L+F) o placebo + fibra dietética (P+F) por 10 días. El estudio fue doble ciego. Del día 10 al 21 los pacientes recibieron solamente la fibra dietética. El objetivo primario de eficacia fue la diferencia en los síntomas entre L+F y P+F utilizando una escala analógica visual calibrada desde 0 a 10. La evaluación se realizó al día 0 y al día 21.

Resultados. La media de todos los síntomas fue significativamente mejorada con L+F y no con P+F. Una significativamente mayor proporción de pacientes con L+F incrementó la escala analógica visual por más de 3 puntos.

Conclusión. La utilización de lincomicina facilitaría el efecto de la fibra dietética por su efecto sobre la flora colónica. La secuencia entre agentes reguladores de la flora colónica + fibra serviría de modelo para remplazar el consumo crónico de medicamentos para la constipación crónica.

Palabras claves. Fibra, antibióticos, lincomicina, constipación crónica.

Chronic constipation is a frequent functional disorder in North America and Western European countries.1,2 In South America, the population of Buenos Aires is 86% of European descent and chronic constipation affects 10% to 27% of this population.3 This pilot trial of chronic constipation was performed in this latter population.

There is no known etiology of chronic constipation. Approved treatments intend to improve symptoms, i.e.,

Estudio controlado piloto sobre la eficacia de una dosis baja de un antibiótico para el tratamiento de la constipación crónica en pacientes con dieta rica en fibra
more frequent bowel movements and easier passage of stools. In the US and Europe approved treatments are pharmacological agents, i.e., lubiprostone, linacolotide, tegaserod, prucalopride. Use of these drugs require uninterrupted daily intake. Treatments are not exempt of side effects. Up to 29% of patients on lubiprostone experimented nausea. In the US, tegaserod was restricted to women up to 50 years of age due to the appearance of ischemic colitis. A high fiber diet is the traditional non-pharmacological treatment for chronic constipation with sometimes inconsistent results. Crude dietary fiber may directly stimulate intestinal peristalsis or indirectly by modifying the colon microbiota. Another way to alter the intestinal microbiota is by the use of antibiotics. Celik et al administered 750 mg of vancomycin to 8 patients with chronic constipation for a period of 14 days. This treatment resulted in a significant improvement of stool frequency, consistency and ease of defecation. Based on this background we designed a controlled pilot study to assess the synergistic short term, low dose, preparatory action of a poorly absorbable antibiotic on chronic constipated patients on a high fiber diet. The macrolide lincomycin was used because it is non-absorbable and with activity against gram positive and anaerobic bacteria. The recommended oral daily dose for systemic infections is 1.5 to 2 g. At these doses, a rare but serious adverse event is pseudomembranous colitis. In Asia, Europe and Latin America, lincomycin is widely available.

**Material and Methods**

**Study design**

This was a randomized, double-blind, placebo controlled study in patients with chronic constipation refractory to conventional therapy. To be eligible, patients had to meet the Rome II diagnostic criteria characterized by a frequency of ≤ 2 bowel movements/week and hard stool, straining with occasional pain in more than 25% of bowel movements. Chronicity was defined as constipation longer than 1 year. Exclusion criteria included cardiac, pulmonary, renal, liver failure, abnormal blood chemistry and known antibiotic allergies. Patients with prior GI surgery were excluded from the study. In patients who were younger than 50 years and had no other complaint than chronic constipation and the physical examination and routine body chemistry were normal, it was assumed the diagnostic of functional constipation and no special gastrointestinal exams were performed. To

**Efficacy parameters and data analyses**

The primary efficacy parameter was the difference between treatments in the mean bowel frequency, straining, stool consistency and pain during defecation at baseline (Day 0) and by the end of treatment period (Day 21). To assess quantitatively differences in the primary efficacy patients were assigned a number on accordance to a validated 10 point visual analogue scale (VAS) of symptom severity (0=very severe, 10=asymptomatic). Post-hoc, we examined the proportion of patients that exhibited marked improvement in the efficacy parameters after the 21 day treatments. Marked improvement was defined by an increase in the VAS ≥ 3 from the baseline value. The paired student t-test was used to estimate significant differences of the primary efficacy endpoint. The Wilcoxon non-parametric test was used to estimate the proportion of patients with differences in stool characteristics.
Results

Demographics and patient disposition
As per protocol, 15 patients were randomized to 500 mg/d lincomycin and 15 patients to placebo. The mean age of patients was 37 ± 16 years old in the lincomycin treatment arm and 41 ± 16 years old in the placebo arm (NS). Both treatment arms included similar proportion of females: 12 in the lincomycin arm and 11 in the placebo arm.

By the end of the treatment period, 27 patients (13 on lincomycin vs. 14 on placebo) had completed the study. One patient on lincomycin was discontinued because of the development of diarrhea. Feces from this patient were negative to the *Clostridium difficile* toxin (ELISA test). He had an uneventful recovery. Another patient on lincomycin was lost-to-follow up. One patient on placebo developed fever of unknown origin and was discontinued from the trial.

Efficacy
None of patients who were treated with the combination of placebo + high fiber exhibited any improvement from baseline in bowel frequency and stool characteristics. In contrast, all patients treated with 10 days lincomycin and 21 days of high dietary fiber showed a significant improvement in bowel frequency, straining, stool consistency and pain sensation (Table 1).

Table 1. Differences in the primary efficacy endpoint before and after treatments.

<table>
<thead>
<tr>
<th></th>
<th>Lincomycin + fiber</th>
<th>Placebo + fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 21</td>
</tr>
<tr>
<td>Frequency</td>
<td>2.6</td>
<td>4.4a</td>
</tr>
<tr>
<td>Straining</td>
<td>2.3</td>
<td>4.4a</td>
</tr>
<tr>
<td>Hard stools</td>
<td>2.3</td>
<td>4.7b</td>
</tr>
<tr>
<td>Pain</td>
<td>4.2</td>
<td>5.7b</td>
</tr>
</tbody>
</table>

a Differences between treatments with values of \( P < 0.02 \).

b Differences between treatments with values of \( P < 0.005 \).

Efficacy outcomes expressed solely by the means may sometimes enhance results. This is so for it may not take into consideration the outliers. Hence, we included another efficacy analysis, i.e., the proportion of patients who reached a significant relief. This analysis, performed customarily in large clinical studies, tends to decrease the relevance of the results but reflect robustness if it shows significance. As seen in Table 2, 33% to 46% of patients on lincomycin and high crude fiber in the diet showed a significant improvement in frequency of bowel movements, straining and stool characteristics. Pain was improved in 20% of patients in this treatment group. None of the patients on placebo and high fiber showed any significant improvement by this analysis.

Table 2. Proportion of patients with visual analogue scale (VAS) increases > 3 points.

<table>
<thead>
<tr>
<th></th>
<th>Lincomycin + fiber</th>
<th>Placebo + fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>5/15 (33%)a</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>Straining</td>
<td>5/15 (33%)</td>
<td>2/15 (13%)</td>
</tr>
<tr>
<td>Hard stools</td>
<td>7/15 (46%)</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>Pain</td>
<td>3/15 (20%)</td>
<td>0/15 (0%)</td>
</tr>
</tbody>
</table>

a All differences between treatments were statistically significant \( P < 0.05 \).

Discussion
This placebo-controlled pilot study examined the efficacy of an initial 10 day low dose lincomycin in a 21 day high crude fiber period in chronic constipated patients. By the end of the 21 day treatment period, the results showed a significantly higher proportion of patients on lincomycin plus high fiber improved their constipation symptoms. The underlying mechanism that led to the effectiveness of this therapy combination was not elucidated in this study. One possibility is a direct action of the lincomycin on the intestinal motility. Lincomycin is a macrolide. Erythromycin, another macrolide, has a proven prokinetic effect on the gastrointestinal tract. The fact that improvement in bowel frequency and stool consistency continued for 11 days after ceasing the lincomycin appears to rule out this effect. A more likely possibility is that the lincomycin effect upon the colon microbiota facilitated a prokinetic activity of the crude fiber. Lincomycin markedly lowers the numbers of strictly gram negative anaerobes as well as gram positive bacteria. Fermentation after loads of crude fiber may also diminished.

In *vitro* experiments have shown that clindamycin inhibits the fermentation of simple sugars by lowering the numbers of the intestinal microbiota.11 Studies in human volunteers revealed that dietary glucose and galactose are recovered intact in stools after administration of 2 g ampicillin.12 Another hypothesis is that the increase in colon peristalsis may have been due to an overgrowth of microorganisms producers of neurotransmitters. Experiments in rats showed that the interaction of a resistant starch with butyrate, a short chain fatty acids produced by the colon microbiota, resulted in an increase in circulatory muscle contractility of the colon.13
This study results do not have the purpose of advocating the use of lincomycin as a preferred antibiotic, though there is a recent resurgence in trials with this macrolide. The authors are aware of the possible risks of the repeated use of antibiotics even if the use is for short periods of time and at non-therapeutic short doses. As stated, pseudo membranous colitis was largely associated with high doses of lincomycin. The association with *Clostridium difficile* infection is widely known as occurring with any antibiotic and with any route of application but is more common in hospitalized patients than in out patients. A low dose of an antibiotic may be justified in chronic constipation refractory to common therapies as a facilitator of the beneficial action of crude fiber. The design and results of this pilot study may serve as a model for the use of similar design with probiotics, a number of which are being intensely investigated in this chronic functional disorder.

Financial Disclosure or Conflict of interest. None

Grant Support. None

References

2. Peppas G, Alexiou VG, Mourtzoukou E, Falagas ME. Epidemiology of constipation in Europe and Oceania: a systematic review. BMC Gastroenterol 2008; www.biomedcentral.com/1471-230X/8/5.