Effect of *Lactobacillus* GG Yoghurt in Prevention of Antibiotic Associated Diarrhoea

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The efficacy of *Lactobacillus* GG yoghurt in preventing erythromycin associated diarrhoea was studied. Sixteen healthy volunteers were given erythromycin acistrate 400 mg t.i.d for a week. The volunteers were randomly assigned into two groups taking twice daily 125 ml of either *Lactobacillus* GG fermented yoghurt or pasteurized regular yoghurt as placebo during the drug treatment.

Subjects receiving *Lactobacillus* GG yoghurt with erythromycin had less diarrhoea than those taking pasteurized yoghurt. Other side effects of erythromycin, such as abdominal distress, stomach pain and flatulence, were less common in the GG yoghurt group than in the placebo yoghurt group.

The subjects receiving *Lactobacillus* GG yoghurt were colonized with these bacteria even during erythromycin treatment as measured by faecal counts of total *Lactobacillus* GG. No *Lactobacillus* GG was found in the faecal samples of volunteers in the group taking pasteurized yoghurt.

Key words: *Lactobacillus* GG; yoghurt; erythromycin; antibiotic diarrhoea.

(Annals of Medicine 22: 57—59, 1990)

Introduction

Antibiotic treatment is often accompanied by diarrhoea and other gastrointestinal side effects. The pathogenesis of antibiotic associated diarrhoea has been related to quantitative and qualitative changes in the intestinal and faecal microflora (1). It has been suggested that prophylactic administration of lactic acid bacteria preparations may prevent diarrhoea (2, 3).

Erythromycin is known to affect the intestinal microflora and to provoke gastrointestinal side effects including nausea, vomiting, abdominal pain and diarrhoea (4, 5). These are symptoms due at least in part to the poor bioavailability and absorption of erythromycin. Erythromycin acistrate, which is the stearate salt of erythromycin containing an acetyl group in the 2 position, is more readily absorbed than other preparations (6, 7). *Lactobacillus* preparations have been used to reconstitute the normal intestinal flora in patients receiving antibiotics who develop treatment related gastrointestinal side effects. *Lactobacillus* GG is a unique *Lactobacillus* strain isolated from a healthy human. This strain was originally selected for its tolerance to acid and bile and the ability to adhere to human small intestinal cells (8). In the present study the preventive effects of *Lactobacillus* GG were investigated on the side effects of erythromycin treatment. The changes in numbers of total lactobacilli, *Lactobacillus* GG and the occurrence of *Clostridium difficile* toxin in faeces were also measured. The study was designed as a randomized placebo controlled study in 16 healthy volunteers.

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Received: July 20, 1989.

Subjects and Methods

Healthy male subjects aged 18—24 years were recruited into the study, they gave written informed consent, and the study was approved by the Ethical Committee of Tampere University Central Hospital. The volunteers were screened using medical records and routine clinical laboratory testing before entering the study. They had not taken any antibiotics during the two months before the study and were not receiving any other medication. The subjects had no known hypersensitivity for erythromycin.

All subjects were randomly assigned to two groups. They received erythromycin acistrate (Erasis tablets, Orion Pharmaceutica, Espoo, Finland) 400 mg t.i.d. for seven days. Half an hour after each morning and evening

dose of erythromycin one group (A) took a 125 ml dose of active *Lactobacillus* GG fermented yoghurt. The other group (B) had a similar portion of pasteurised placebo yoghurt fermented with *Streptococcus thermophilus* and *Lactobacillus bulgaricus* with no live bacteria present.

Subjective symptoms were followed on personally completed daily records and by an interview with a physician before and after the study. The results of observations on the side effects were analyzed statistically using the Chi-square and Student's t-tests.

On the first and last days of both treatments, six volunteers gave blood samples to obtain serum for erythromycin determination with samples taken at the start of treatment and one, two, three, four and six hours after drug intake. The sera were separated and stored at —18°C until the drug concentration assay. Food was allowed after the 3-hour sample. Erythromycin concentrations in serum were analysed microbiologically as described earlier (9).

Stool specimens were taken on the first and last day of treatment. Stools were collected in sterile plastic bags, weights were recorded and samples were frozen immediately and delivered to the laboratory.

The total number of lactobacilli and the number of *Lactobacillus* GG were analysed on Lactobacilli MRS agar (Difco nr. 0881-01, Detroit, USA). The plates were incubated anaerobically for 72 hours at 37°C. (Anaerocult A, Merck nr. 13829, Darmstadt, FRG). The plates were evaluated initially by examining the different colony types. The GG strain produces large white and creamy colonies on MRS agar. Typical colonies were purified to check for cell morphology and lactose fermentation. *Lactobacillus* GG are lactose negative, gram positive rods of uniform shape, grouped mainly in chains. The final identification of isolates was based on carbohydrate fermentations (API 50 CHL, API system S.A. France). The presence of *Clostridium difficile* toxin was analysed using Willey and Bartlett's method (10).

Results

The incidence of diarrhoea was significantly lower ($P < 0.05$) in the GG yoghurt group (two days) than in the placebo yoghurt group (eight days). The total incidence of reported stomach pain was 23 % in the GG group and 39 % in the placebo group. Furthermore, the incidence of diffuse abdominal pain and nausea was smaller in the GG yoghurt group than in the placebo group. The number of daily defecations was fewer in the *Lactobacillus* GG than in the placebo group. The difference in the faecal volumes measured on the first and seventh day was not statistically significant between the groups (data not shown).

The count of faecal lactobacilli was not significantly altered during erythromycin treatment (Fig. 1A). No identifiable *Lactobacillus* GG was found in the faeces of volunteers receiving the placebo yoghurt, but samples from most volunteers (75 %) receiving *Lactobacillus* GG yoghurt showed detectable numbers (detection limit 10^3 cfu/g, Fig. 1B). Volunteers who because of constipation produced their first samples on the second day had *Lactobacillus* GG already present in their faeces. No cases of *Clostridium difficile* toxin were found.

Serum levels of erythromycin produced by erythromycin acistrate are shown in Figure 2. The concentrations did not differ significantly although on day one the maximum level was reached three hours later in the GG group than in the placebo group. On day seven the erythromycin concentration was slightly higher in the GG group than in the placebo group.

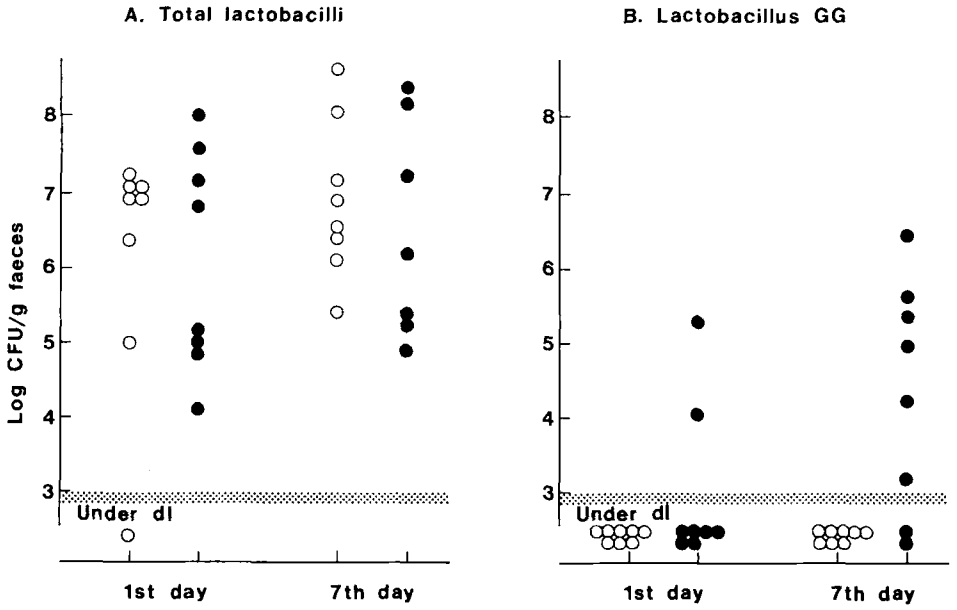

Figure 1. The number of total lactobacilli (A) and *Lactobacillus* GG (B) in faeces samples of subjects receiving placebo yoghurt (○) or *Lactobacillus* GG yoghurt (●) on days one and seven. dl = detection limit.

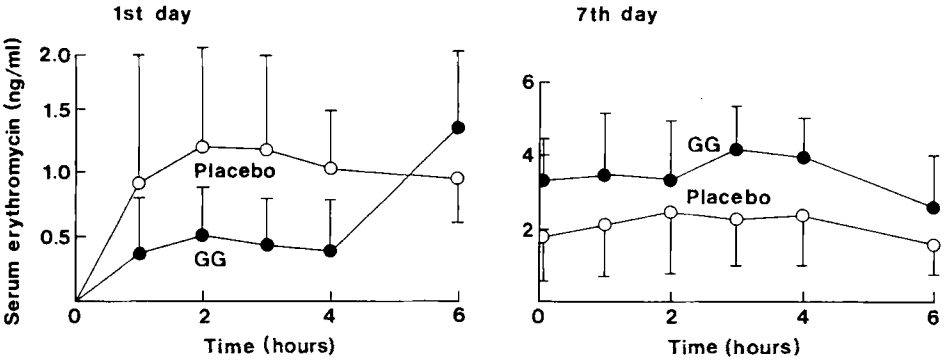

Figure 2. Serum erythromycin concentrations after a 400 mg erythromycin acistrate administration followed by a 125 ml dose of placebo yoghurt (○—○) or *Lactobacillus* GG yoghurt (●—●). Day one indicates the first tablet of treatment and day seven the steady state of erythromycin treatment (N = six in each group).

Discussion

The administration of antibiotics is often accompanied by diarrhoea and other gastrointestinal side effects. Oral antibiotics alter the intestinal flora, so administration of lactic acid bacteria has been suggested as a way of reducing such side effects. Treatment with *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* in a freeze dried form has previously been shown to reduce the frequency of gastrointestinal disorders. Based on a fall of clostridial spore counts, the test product was also thought to reduce alteration in intestinal microflora (11).

In the present study the incidence of diarrhoea was significantly reduced in the group that received *Lactobacillus* GG. Other *Lactobacillus* preparations have been used with some success to prevent antibiotic diarrhoea (2, 11). Some of the effects, however, have been controversial (11) and more effective results have been obtained in balancing the microflora by oral administration of lactobacilli (3).

Initially serum concentrations of erythromycin were slightly lower in volunteers receiving *Lactobacillus* GG than in the placebo yoghurt group. The situation was reversed, however, in six hours and also when the steady state was reached as indicated for the seventh day.

This study suggests that *Lactobacillus* GG yoghurt may have the potential for preventing erythromycin associated gastrointestinal side effects, especially diarrhoea. *Lactobacillus* GG is also able to colonize the intestinal tract despite antibiotic treatment, and it may thereby help to restore the normal intestinal microflora during and after erythromycin therapy.

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