LACTEOL FORT TREATMENT REDUCES ANTIBIOTIC ASSOCIATED DIARRHEA

Dr Yap Soo Kor Jason, A/Prof Gwee Kok Ann, Chen Zhaojin, A/Prof Tai Bee Choo, A/Prof Wong Mee Lian

ABSTRACT

Background: Antibiotic treatment is commonly associated with gastrointestinal symptoms, in particular diarrhea. The use of lactobacillus preparation has been proposed as a preventive measure.

Objectives: We conducted an exploratory study on the effect of Lacteol fort (LF), a heat inactivated lactobacillus preparation, on antibiotic associated bowel disturbances in a primary care population.

Methods: Consecutive patients attending a primary care clinic because of infection and who were prescribed antibiotics were recruited prospectively. All patients seen by one attending physician were prescribed antibiotics without LF (antibiotic only) (n=96, 29% male, mean age 38 years), while all patients seen by another attending physician were prescribed 2 LF capsules bd for one week during the antibiotic treatment course (antibiotic+LF) (n=88, 43% male, mean age 36.4 years). From the same centre, healthy patients attending the annual health screening (healthy controls) (n=141, 23% male, mean age 39.7 years) were also enrolled in the study. All subjects completed a structured questionnaire at entry, and kept a bowel diary for two weeks from the start of treatment.

Results: More patients who received antibiotic treatment reported loose stools ≥ 1 day than healthy subjects who had not received antibiotics, but diarrhea was less in the Lacteol fort treated group (antibiotic only: RR = 1.36, 95% CI 1.07 – 1.72; antibiotic+LF: RR = 1.16, 95% CI 0.89 – 1.51, p=0.046). LF did not reduce the risk of developing bloating, flatus and abdominal pain among patients given antibiotics.

Conclusion: Our results suggest that Lacteol fort treatment may reduce the risks of diarrhea associated with antibiotic treatment.

Keywords: lactobacillus, antibiotic, diarrhea, probiotic

YAP SOO KOR JASON, Head, Training & Development at ParkwayShenton, Adjunct Assistant Professor at Duke-NUS Shenton Medical Group

GWEE KOK ANN, Gastroenterologist at Gleneagles Hospital, Adjunct Associate Professor of Medicine at the National University of Singapore, and Visiting Consultant, National University Hospital Stomach Liver & Bowel Clinic, Gleneagles Hospital

CHEN ZHAOJIN, Research Assistant, Dept of Epidemiology & Public Health, NUS

TAI BEE CHOO, Associate Professor, Dept of Epidemiology & Public Health, NUS

WONG MEE LIAN, Associate Professor, Dept of Epidemiology & Public Health, NUS

SFP2010; 36(4): 46-49

INTRODUCTION

Diarrhea is the commonly reported side effect of antibiotic treatment for non-gastrointestinal infections.[1-3] In an earlier prospective study of 200 patients receiving antibiotics from our clinic, loose stools and bloating were reported significantly more frequently than in controls who had not received antibiotics.[4]

Disturbance of the normal gastrointestinal microflora is a possible mechanism for the development of diarrhea, and treatment with probiotic microorganisms such as lactobacilli, has been proposed as a preventive measure. However, there is a perception that antibiotic treatment may affect the viability of probiotic bacteria. The aim of this study was to examine the effects of Lacteol fort (LF), a heat inactivated lactobacillus preparation lactobacillus preparation, on antibiotic associated diarrhea. A secondary objective was to study its effects on other bowel symptoms. LF was chosen for this study because it is on the clinic's standard list, and is indicated for the treatment of diarrhea. This study also gave us the opportunity to estimate the prevalence of irritable bowel syndrome (IBS) in our patient population.

MATERIALS AND METHODS

Subjects

In this study, we prospectively recruited consecutive patients who were prescribed antibiotics in our primary care clinic and healthy patients attending their annual health screening. The following were exclusion criteria:

(1) History of recurrent diarrhea, functional dyspepsia or irritable bowel syndrome (IBS)
(2) History of peptic ulcer or major abdominal surgery
(3) History of psychiatric illness
(4) Pregnancy
(5) Immuno-compromised states eg patients on steroid or chemotherapy
(6) Had received antibiotics 1 month or less before the start of the study
(7) Current prescription of antibiotics for a gastrointestinal illness.

Response to recruitment was 75%. Those who declined to participate were mainly young executives in higher management level who had frequent business travel or overseas assignments. Of the 184 patients who required antibiotic therapy, the majority 111 (60.3%) were given for upper respiratory tract infections and the remaining 73 (39.7%) were for skin sepsis, urinary tract infections, ENT conditions and other infections. Penicillins accounted for 108 patients (58.7%), macrolides 52 patients (28.3%) and other antibiotics 24 patients (13.0%).

Study design

The study protocol was approved by the institutional review board, and written informed consent was obtained from every patient before enrollment.

All patients receiving treatment from one attending physician were prescribed antibiotics without LF (antibiotic only), while all patients receiving treatment from another attending physician were prescribed two LF capsules bd for one week during the antibiotic treatment course (antibiotic+LF). From the same centre, healthy patients attending annual health screening (healthy controls) were invited to participate only in the assessment procedures. Eligible patients completed a baseline validated structured questionnaire and kept a bowel diary for two weeks from the time of recruitment.

Assessment procedures

At entry, a previously validated structured questionnaire was administered to each patient via a face-to-face interview by a research assistant.[4] Patients' demographic details, reasons for attendance, the type of antibiotics prescribed, the presence of abdominal pain, bloating, flatulence, and the patients' normal bowel habit, including the frequency and consistency of their stools, were recorded. Symptoms were defined as being present when they occurred more than 25% of the time. Irritable bowel syndrome (IBS) was defined by the Rome II criteria.

All patients were also requested to complete a 2-week bowel diary. Careful instructions were given on how to fill up the diary which recorded stool timing and stool consistency, occurrence of abdominal pain, bloating and flatulence. The diary was returned to the clinic at the end of 2 weeks. A Bristol Stool Scale was also given to avoid ambiguity in reporting.[5]

Outcome Measures

Outcome measures were defined as the incidence of bowel symptoms (abdominal pain, bloating, change in stool frequency, and change in stool consistency) in patients during the 2 weeks after recruitment into the study. In addition to the development of specific symptoms, the frequency of experiencing such symptoms was compared between cases and controls. The primary endpoint was the number of days with loose stools during the 2 weeks of diary recording.

Statistical Analysis

Demographic data was summarised in terms of frequency and percentages in the case of categorical variables, and expressed as mean and standard deviation for continuous variables.

Inter-group comparison of proportions was performed using the Pearson chi-square, with effect measure presented in terms of relative risk (RR) and its associated 95% confidence interval (CI). Further analysis was carried out to account for potential confounding effect of age and baseline IBS on the outcomes. Statistical evaluations were made assuming a two-sided test based on a 5% level of significance. The STATA (Version 11) software was used for all statistical analysis.

Results

A total of 325 patients were recruited: 96 antibiotic only (29% male, mean age 38 years), 88 antibiotic+LF (43% male, mean age 36.4 years), and 141 healthy controls (23% male, mean age 39.7 years) (Table I). The prevalence of IBS at baseline was 33% for antibiotic only, 30% for antibiotic+LF and 21% for healthy controls (p = 0.111). However, patients on antibiotics with or without LF were at higher risk of IBS at baseline as compared with healthy controls (RR = 1.53; 95% CI 1.01 to 2.33, p = 0.039).

More patients who received antibiotic treatment reported loose stools ≥ 1 day than subjects who did not receive antibiotics (antibiotic only: crude RR = 1.36, 95% CI 1.07 – 1.72; antibiotic+LF: crude RR = 1.16, 95% CI 0.89 – 1.51; p = 0.046) but fewer had diarrhea in the antibiotic+LF group (Table II). Adjusting for the potential confounding effect of age and baseline IBS, the results remained unaltered (antibiotic only: adjusted RR: 1.32, 95% CI 1.03 – 1.70; antibiotic+LF: adjusted RR = 1.14; 95% CI 0.86 – 1.51). The number of days with loose stools was significantly greater in patients not receiving LF, than healthy controls (antibiotic only 2.39 days, healthy 1.53 days, p=0.03). LF did not significantly reduce the

Table I: Demographic characteristics of study subjects by treatment

	Anitbiotic only (n = 96)	Antibiotic + LF (n = 88)	Healthy controls (n = 141)
Mean age (SD)	38.0 (9.3)	36.4 (8.4)	39.7 (8.8)
Gender (%)			
Male	28 (29.2)	38 (43.2)	32 (22.7)
Female	68 (70.8)	50 (56.8)	109 (77.3)
Race (%)			
Chinese	85 (88.6)	79 (89.8)	126 (90.6)
Malay	7 (7.3)	4 (4.6)	6 (4.3)
Indian	3 (3.1)	2 (2.3)	5 (3.6)
Other	1 (1.0)	3 (3.3)	2 (1.5)
Baseline IBS	32 (33.3)	27 (30.1)	23 (20.9)

Note: All 325 subjects completed baseline questionnaire and baseline bowel diary.

risk of developing bloating, flatus and abdominal pain among patients given antibiotics although there appeared to be a trend (Tables III to V).

Table II : Prevalence of loose stool ≥ 1 day by treatment

	Prevalence (%)	Crude RR (95% CI)	p-value
Treatment (%)			0.046
Healthy controls	65 (46.1)	1.00	-
Antibiotics + LF	47 (53.4)	1.16 (0.89 – 1.51)	0.282
Antibiotics only	60 (62.5)	1.36 (1.07 – 1.72)	0.013

Table III : Prevalence of bloating by treatment

	Prevalence (%)	Crude RR (95% CI)	p-value
Treatment (%)			0.195
Healthy controls	16 (11.5)	1.00	
Antibiotics + LF	10 (11.5)	1.00 (0.47 – 2.10)	0.997
Antibiotics only	18 (19.1)	1.66 (0.89 – 3.09)	0.105

Table IV : Prevalence of flatus by treatment

	Prevalence (%)	Crude RR (95% CI)	p-value
Treatment (%)			0.421
Healthy controls	27 (19.6)	1.00	
Antibiotics + LF	21 (25.6)	1.31 (0.79 – 2.16)	0.294
Antibiotics only	25 (26.0)	1.33 (0.83 – 2.15)	0.241

Table V : Prevalence of abdominal pain by treatment

	Prevalence	Crude RR(95% CI)	p-value
Treatment (%)			0.517
Healthy controls	10 (7.1)	1.00	
Antibiotics + LF	3 (3.5)	0.49 (0.14 – 1.73)	0.252
Antibiotics only	6 (6.4)	0.89 (0.34 – 2.38)	0.821

DISCUSSION

In a previous prospective study conducted in our primary care clinic, we found that significantly more patients prescribed antibiotics reported gastrointestinal symptoms than healthy controls.[4] In that study, the prevalence of gastrointestinal symptoms reported amongst 200 antibiotic treated patients were: loose stools 11.5% , abdominal pain 3%, bloating 3.5% and hard stools 8.5%. In contrast, amongst the 600 healthy controls, the prevalences were : loose stools 1.5%, abdominal pain 1.2%, bloating 1.0% and hard stools 1.0%. As in our earlier study, we found in our present study that diarrhea was the commonest bowel disturbance.

Of note is that in this cohort of executives working in the Central Business District where the clinic is situated, there was a substantial number of healthy subjects reporting bowel symptoms such as abdominal pain, bloating, flatulence, and especially loose stools. Even though we had excluded patients with a known diagnosis of irritable bowel syndrome, we found a high prevalence of patients who met Rome II criteria for IBS at baseline. In our present study, the 20.9% prevalence of Rome II criteria for IBS in the patients attending for health screening gives us an estimate of the IBS prevalence in a primary care setting. In an early study from a local tertiary hospital, IBS by clinical criteria accounted for 17% of new patients referred to the gastroenterology clinic.[6] In our community survey, we found a prevalence of 8.6% by Rome II criteria.[7] These observations suggest that there is a high background prevalence of pre-existing bowel symptoms in our study population, and this may predispose to the development of antibiotic associated symptoms. However, even after controlling for baseline IBS, we found that patients receiving antibiotic treatment reported significantly more bowel symptoms in prospective diary recordings.

We selected Lacteol fort for our study because it is one of the earliest lactobacillus formulation introduced in Singapore for the treatment of diarrhea and is therefore widely prescribed by family doctors and available over the counter to patients. However it is not considered to be a probiotic because the definition of a probiotic formulation is that the contents include live micro-organisms, whereas Lacteol fort consists of heat-killed Lactobacillus bacteria. The therapeutic effects of Lacteol fort have been attributed to its protective properties, including adhesion, to colonize the human intestinal absorptive and mucosecretory cells. It hides the receptor sites of pathogenic germs and prevents their adhesion.[8-10] The use of fermented culture medium of LF alone was capable of inhibiting cellular injuries and intracellular growth of pathogens.[11]

In our study, we observed that LF may reduce the risk of diarrhea among those who were prescribed antibiotics. In addition to the effect on loose stools, there was also a trend for LF treatment to improve symptoms of abdominal pain, flatulence and bloating. We recognize the limitations of an unblinded study, in particular the possibility of a placebo effect. However, our primary endpoint, ie loose stools defined by the Bristol stool scale and based on recordings in a bowel diary, is a fairly robust one that is less open to subjective perception as is the case with symptoms like bloating, flatus and abdominal pain.

There is also evidence from in-vitro research to suggest that live bacterial organisms are not necessarily critical for the therapeutic effects of probiotic agents. In a study employing a mouse-model of post-infectious irritable bowel syndrome, it was demonstrated that treatment with live Lactobacillus paracasei could attenuate the inflammatory and motility changes observed in the intestines arising from infection with the Trichinella spiralis nematode. Of particular interest, was that treatment with the spent culture medium for Lactobacillus paracasei (in the absence of live organisms) was able to provide almost identical anti-inflammatory protection and improvement in muscle contractility.[12]

CONCLUSION

Our observation that concomitant treatment of Lacteol fort with antibiotic may reduce the risks of developing diarrhea, suggests that live lactobacillus containing preparations may not be essential for therapeutic effects, and that treatment may be viable in the presence of antibiotics.

REFERENCES

1. Wiström J, Norrby SR, Myhre EB, et al. Frequency of antibiotic associated diarrhoea in 2462 antibiotic-treated hospitalized patients: a prospective study. J Antimicrob Chemother 2001; 47:43-50.

2. McFarland LV. Epidemiology, risk factors and treatments for antibiotic associated diarrhoea. Dig Dis 1998; 16:292-307.

3. Bartlett JG, Chang TW, Gurwith M, et al. Antibiotic-associated pseudomembranous colitis due to toxin producing Clostridia. N Engl J Med 1978; 298:531-4.

4. Jason Yap Soo Kor, Gwee Kok Ann, Joel Hwan Ern Huei, et al. Antibiotic associated bowel disturbances in a young healthy primary care population. Singapore Family Physician 2006; 32(2):54-8.

5. Heaton KW, Ghosh S, Braddon FEM. How bad are the symptoms and bowel dysfunction of patients with irritable bowel syndrome? A prospective study with emphasis on stool form. Gut 1991;32:73-9.

6. Kang JY, Yap I, Gwee KA. The pattern of functional and organic disorders in an Asian gastroenterological clinic. J Gastroenterol Hepatol 1994;9:124-7.

7. Gwee KA, Wee S, Wong ML, et al. The Prevalence, Symptom Characteristics and Impact of Irritable Bowel Syndrome in an Asian Urban Community. Am J Gastroenterology 2004;99:924-31.

8. Chauviere G, Coconnier MH, Kerneis S, et al. Adhesion of human Lactobacillus acidophilus strain LB to human enterocyte-like Caco-2 cells. J Gen Microbiol. 1992;138(pt 8):1689-96.

9. Chauviere G, Coconnier MH, Kerneis S, et al. Competitive exclusion of diarrheagenic Escherichia coli (ETEC) from human enterocyte-like Caco-2 cells by heat-killed Lactobacillus. FEMS Microl Lett. 1992;70:213-7.

10. Coconnier MH, Bernet MF, Kerneis S, et al. Inhibition of enteroinvasive pathogens to human intestinal Caco-2 cells by Lactobacillus acidophilus strain LB decreases bacterial invasion. FEMS Microbiol Lett. 1993; Jul 1;110(3):299-305.

11. Coconnier MH, Levin V, Lorrot M, et al. Antagonistic activity of Lactobacillus acidophilus LB against intracellular Salmonella enteric serovar Typhiruium infecting human enterocyte-like Caco-2/TC-7 cells. Appl Environ Microbiol. 2006;66:1152-7.

12. Elena F, Verdu, Premysl Bercik et al. Lactobacillus paracasei Normalizes Muscle Hypercontractility in a Murine Model of Postinfective Gut Dysfunction. Gastroenterology 2004; 127:826-37.