ANTIBIOTIC ASSOCIATED BOWEL DISTURBANCES IN A YOUNG HEALTHY PRIMARY CARE POPULATION

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ABSTRACT

Objective: **Gastrointestinal symptoms are perceived to be common complaints arising from the use of antibiotics. This prospective study examines the association between antibiotics and the gastrointestinal symptoms of pain, bloating, hard stools and loose stools in a primary care population.**

Subjects and Methods: **Over a two-month period, 200 consecutive outpatients (cases) who were prescribed antibiotics (46% male, mean age 37±9.3 years) and 600 consecutive healthy subjects (controls) who came for pre-employment check-ups and screening (44% male, mean age 32±9.9 years) were enrolled in the study. A structured questionnaire was administered at face-to-face interview and repeated 2 weeks later by telephone interview.**

Results: **The frequency of symptoms was: pain 3.0%, bloating 3.5%, hard stools 8.5%, and loose stools 11.5%. Cases were 3.4, 7.4 and 9.3 times more likely to develop abdominal bloating, loose stools and hard stools respectively as compared to controls. The frequency of respondents who met Rome II criteria of irritable bowel syndrome (IBS) was 4.5%.**

Conclusions: **Patients who were given a course of antibiotics had increased risk of developing bowel disturbances as compared to patients who were not given antibiotics. Patients could develop antibiotic associated constipation rather than diarrhoea. Furthermore, some patients developed symptoms consistent with irritable bowel syndrome. Further longitudinal study is needed to confirm the association of IBS with antibiotic use.**

Keywords: diarrhoea, constipation, incidence, antibiotics, primary care

INTRODUCTION

Diarrhoea is a common adverse effect of antibiotic treatment. Antibiotic associated diarrhoea (AAD) occurs in about 5-30% of patients either early during antibiotic therapy or up to two months after the end of the treatment[1-3]. The frequency of antibiotic associated diarrhoea depends on the definition of diarrhoea, the inciting antimicrobial agents, and host factors[4].

While AAD is well recognized, other bowel disturbances are less well studied. The association between antibiotic use and symptoms of IBS, namely, abdominal pain or discomfort associated with altered defaecation or change in bowel habits, has been suggested in a small number of studies[5-7].

We therefore conducted a prospective study to ascertain the risks of bowel disturbances in the immediate two weeks following the use of antibiotics. Our hypothesis is that a course of antibiotics is a risk factor in the development of gastrointestinal symptoms of abdominal pain, bloating, hard stools and loose stools.

MATERIALS AND METHODS

Subject Selection

Over a two-month period between March and April 2005, two hundred adult outpatients who were given antibiotic therapy (cases) for various clinical indications were recruited consecutively. During the same period, 600 consecutive healthy subjects attending the same clinic for routine and employment required health screening were recruited as controls. Response to recruitment was 95%. Those who declined to participate were mainly young executives in higher management level who had frequent business travel or overseas assignments.

Patients were excluded from the study, if they had one or more of the following:

(1) History of diarrhoea, functional dyspepsia or irritable bowel syndrome (IBS)
(2) History of peptic ulcer or major abdominal surgery who may present with bowel symptoms
(3) History of psychiatric illness
(4) Female patients who were pregnant
(5) Immuno-compromised patients who were on steroid or chemotherapy
(6) Patients who were given antibiotics 1 month or less before the start of the study
(7) Patients receiving antibiotics for gastrointestinal illness

Structured Questionnaire

Informed consent was obtained from patients before they were interviewed. A structured detailed questionnaire was administered at face-to-face interviews to the patients by 2 research nurses and repeated 2 weeks later by telephone interview. In addition to recording the patients' demographic details, reasons for attendance, and the antibiotics prescribed,

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patients' bowel symptoms were assessed using a previously validated structured questionnaire[8] at the clinic. The questionnaire included questions on the presence of abdominal pain and bloating and the association of these symptoms with change in bowel consistency and frequency. There were also questions on the normal bowel habit of patients, including the frequency and consistency of stool. Symptoms were defined as being present when they occurred greater than 25% of the time.

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 in the 2 weeks after recruitment into the study population. In addition to development of the various specific symptoms, analysis was also carried out to compare the number of symptoms experienced between cases and controls.

Statistical Analysis

Demographic data was analyzed with descriptive statistics and expressed as mean ± standard deviation. As the control group differed significantly in the age group and also ethnicity, the following were done: (1) the control group was adjusted for age, and (2) comparison analyses were done with all the respondents as well as only in the majority ethnic group, namely the Chinese.

Inter-group comparison of proportions was performed by using either the Pearson chi-square or Fisher's exact test as appropriate. Comparison of means was carried out using the t-test. Level of significance was set at 0.05 and 95% confidence intervals (95% CI) were computed. Cox's proportional hazards regression model was used to determine the relative risk of developing bowel disturbances (the outcome measure) by having taken antibiotics or not (exposure variable) adjusted for confounders such as age. The Statistical Package for the Social Sciences for Windows (Version 13) was used for all statistical analysis.

RESULTS

Study Population Demographic Characteristics and Response Rates

Eight hundred subjects (200 antibiotic cases and 600 controls) were recruited in the prospective study and a 100% response was achieved at the 2-week follow-up telephone interview. The response rate of the study group was 100%. The response rate of the control group was 95%.

Table 1 compares the demographic characteristics of the two groups. There was no significant difference on gender. The antibiotic treatment group was 4.6 years older in mean age ($p<0.001$). A significantly higher proportion of respondents who were treated with antibiotic consisted of Caucasian and other races (Japanese, Korean and Filipinos) as compared to controls, and a higher proportion of Indian nationals were among the controls.

Antibiotic use

The majority (90%) of patients was prescribed antibiotics for a duration of 5 days, and for upper respiratory tract infection (URTI). Penicillins such as amoxicillin (60%), and macrolides such as erythromycin and clarithromycin (30%), accounted for the bulk of antibiotics prescribed (Table 2).

Gastrointestinal Symptoms

Table 3 shows the reported incidence and relative risks (RRs) of bowel symptoms in cases versus controls at the 2-week follow-up. A higher proportion of cases than controls reported bowel symptoms such as pain, bloating, loose and hard stools. 3.0% and 3.5% of cases reported new onset of abdominal pain and bloating respectively as compared to 1.2% and 1.0% of controls, giving adjusted RRs of 2.43 and 3.44 for abdominal pain and bloating respectively. The most frequently reported symptom by cases (patients on antibiotics) was loose stools with 11.5% of them reporting this symptom compared to 1.5% of those not on antibiotics

Table 1. Demographic Data for Patients

	Patient cohort on antibiotics (n=200)	Control cohort not on antibiotics (n=600)	p values
Sex:			
Male (No, %)	92 (46%)	266 (44.3%)	p=0.68
Female (No, %)	108 (54%)	334 (55.7%)	
Race:			
Chinese (No, %)	149 (74.5)	473 (78.8)	
Indian (No, %)	14 (7.0)	68 (11.3)	
Malay (No, %)	16 (8.0)	33 (5.5)	p=0.001
Eurasian (No, %)	3 (1.5)	5 (0.8)	
Caucasian (No, %)	7 (3.5)	2 (0.3)	
Others (No, %)	11 (5.5)	19 (3.2)	
Age (Mean ± sd)	37.0±9.3	32.4±9.9	p<0.001

Table 2. Distribution of Antibiotics Prescribed and Presenting Complaints

Antibiotic	Diagnostic Group					Total
	URTI	Skin sepsis	ENT	UTI	Others	
Penicillins (%)	94 (60.3%)	13 (59.1%)	6 (54.5%)	1 (50.0%)	3 (33.3%)	117 (58.5%)
Macrolides (%)	49 (31.4%)	2 (9.1%)	3 (27.3%)	0 (0%)	2 (22.2%)	56 (28.0%)
Tetracylines (%)	7 (4.5%)	6 (27.3%)	0 (0%)	0 (0%)	2 (22.2%)	15 (7.5%)
Quinolones (%)	1 (0.6%)	0 (0%)	2 (18.2%)	0 (0%)	0 (0%)	3 (1.5%)
Cephalosporins (%)	1 (0.6%)	1 (4.5%)	0 (0%)	1 (50.0%)	0 (0%)	3 (1.5%)
Co-trimoxazole (%)	4 (2.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (2.0%)
Metronidazole (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (11.1%)	1 (0.5%)
Cipro+Flagyl (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (11.1%)	1 (0.5%)
Total (%)	156 (100.0%)	22 (100.0%)	11 (100.0%)	2 (100.0%)	9 (100.0%)	200 (100.0%)

Table 3. Distribution of Bowel Symptoms Among Cases and Controls at 2-week Follow-up (All Patients)

	No (%) Patients on antibiotics reporting symptoms (n=200)	No (%) Controls not on antibiotics reporting symptoms (n=600)	*RR (95% CI)	p value	Adjusted (95% CI)	RR p value
Pain: Wk2 (No %)	6 (3.0)	7 (1.2)	2.62 (0.87-7.89)	p=0.08	2.43 (0.80-7.42)	p=0.12
Bloating: Wk2 (No %)	7 (3.5)	6 (1.0)	3.59 (1.19-10.81)	p<0.02	3.44 (1.12-10.53)	p=0.03
<3 stools/wk: Wk2 (No %)	1 (0.5)	0 (0)	na	p=0.08	-	-
>3 stools/day: Wk2 (No %)	0 (0)	2 (0.3)	na	p=0.41	-	-
Loose stools: Wk2 (No %)	23 (11.5)	9 (1.5)	8.53 (3.88-18.78)	p<0.01	7.37 (3.35-16.21)	p<0.01
Hard Stools: Wk2 (No %)	17 (8.5)	6 (1.0)	9.20 (3.57-23.67)	p<0.01	9.25 (3.56-24.03)	p<0.01
1 or more symptoms: Wk2 (No %)	33 (16.5)	21 (3.5)	5.45 (3.07-9.67)	p<0.001	4.71(2.73-8.15)	p<0.001
2 or more symptoms: Wk2 (No %)	14 (7.0)	6 (1.0)	7.45 (2.82-19.67)	p<0.001	7.00(2.69-18.22)	p<0.001
Met Rome II criteria: Wk2 (No %)	9 (4.5)	2 (0.3)	14.09 (3.02-65.77)	p<0.001	13.50(2.92-62.48)	p<0.001

*The *relative risk denotes the percentage who develops bowel symptoms in cases divided by the percentage developing symptoms in controls.*

(adjusted RR 7.4). However, the greatest relative risk that cases faced over controls was the development of hard stools which occurred in 8.5% of cases and 1.0% of controls, giving an adjusted RR of 9.3. Fourteen patients (7%) receiving antibiotics developed two or more bowel symptoms as compared to 6 (1%) controls.

A significantly higher proportion of cases met Rome II criteria for IBS at week 2 as compared to controls. 4.5% of cases met Rome II criteria for IBS as compared to 0.3% of controls, giving an adjusted RR of 13.50. The Rome II criteria of IBS include presenting with abdominal pain or discomfort plus at least two of the following: relieved by defecation, and/or associated with a change in frequency of stool, and/or associated with a change in the form of stool.

Data adjustments

To adjust for the confounding because of the difference in ethnic distribution seen in the treatment and control groups, analysis of the data using the majority race, Chinese, was carried out and the results are shown in Table 4.

Table 4. Distribution of Bowel Symptoms Among Cases and Controls at 2-week Follow-up (Chinese Only)

	No (%) Patients on antibiotics reporting symptoms (n=200)	No (%) Controls not on antibiotics reporting symptoms (n=600)	*RR (95% CI)	p value	Adjusted RR (95% CI)	p value
Pain: Wk2 (No %)	4 (2.7)	6 (1.3)	2.15 (0.60-7.71)	p=0.23	2.12(0.60-7.50)	p=0.25
Bloating: Wk2 (No %)	6 (4.0)	6 (1.3)	3.27 (1.04-10.28)	p=0.03	3.17(1.02-9.84)	p<0.05
<3 stools/week: Wk2 (No %)	1 (0.7)	0 (0)	na	p=0.24	-	-
>3 stools/day: Wk2 (No %)	0 (0)	2 (0.4)	na	p=1	-	-
Loose stools: Wk2 (No %)	19 (12.8)	9 (1.9)	7.54(3.33-17.05)	p<0.001	6.70(3.03-14.81)	p<0.001
Hard Stools: Wk2 (No %)	15 (10.1)	6 (1.3)	8.71 (3.12-22.89)	p<0.001	7.94(3.08-24.45)	p<0.001
1 or more symptoms: Wk2 (No %)	27 (18.1)	20 (4.2)	5.01(2.72-9.24)	p<0.001	4.29(2.40-7.64)	p<0.001
2 or more symptoms: Wk2 (No %)	12 (8.1)	6 (1.3)	6.82(2.51-18.50)	p<0.001	6.35(2.38-16.91)	p<0.001
Met Rome II criteria: Wk2 (No %)	7 (4.7)	2 (0.4)	11.61(2.39-56.51)	p<0.001	11.11(2.31-53.48)	p<0.01

The results showed that the exclusion of other races did not alter the significance of the results. A higher proportion of cases than controls still reported gastrointestinal symptoms of pain, bloating, loose and hard stools. A frequency of 2.7% of cases reported new onset of abdominal as compared to 1.3% of controls, giving adjusted RRs of 2.12 (not significant). 4.0%, 12.8% and 10.1% of cases reported new onset of bloating, loose stools and hard stools respectively, compared to 1.3%, 1.9% and 1.3% of controls. The adjusted RRs were 3.17, 6.70 and 7.94 for onset of bloating, loose stools and hard stools respectively. Twelve patients (8.1%) receiving antibiotics developed two or more bowel symptoms as compared to 6 (1.3%) controls. A higher proportion of cases met Rome II criteria for IBS at week 2 as compared to controls, namely 4.7% of cases met Rome II criteria for IBS as compared to 0.4% of controls. This gave an adjusted RR of 11.11 (Table 3).

DISCUSSION

The frequency of bowel symptoms in 200 patients who used antibiotics was: pain 3.0%, bloating 3.5%, hard stools 8.5%, and loose stools 11.5%. Cases were 3.4, 7.4 and 9.3 times more likely to develop abdominal bloating, loose stools and hard stools respectively as compared to controls. The frequency of respondents who met Rome II criteria was 4.5%.

It confirmed the most commonly observed adverse effect is antibiotic associated diarrhoea (AAD). Two main classes of antibiotics were prescribed to patients in this study. The penicillin class has a broad spectrum and is well known to predispose to the development of diarrhoea. Penicillin associated diarrhoea is thought to result from disruption of the normal microflora of the gut. The other major class of antibiotics encountered in our study was the macrolide antibiotics. These antibiotics, particularly erythromycin, have activity on motilin receptors which promote intestinal motility[9,10]. It is possible that a promotility effect could have contributed to the development of diarrhoea in some of our patients. In most cases of AAD, discontinuation or replacement of the inciting antibiotic with another drug of lower AAD risk can be effective.

Hard stools from antibiotic use have not been reported as far as we know. This suggests that while in some patients antibiotic treatment could encourage the development of diarrhoea, in other patients it could promote the development of constipation. Just as with antibiotic associated diarrhoea, it is possible that a disturbance of colonic flora could be a pathogenic mechanism for the development of constipation. Two earlier studies had reported dramatic improvement in a small number of patients with longstanding previously intractable chronic constipation following treatment with a short course of antibiotics[11,12]. In both studies, vancomycin, a non-absorbable broad spectrum antibiotic, was administered orally. In one study, motility assessment limited to measurement of small intestinal transit time by hydrogen breath testing suggested that the response was not related to a prokinetic effect[11]. In the other study, sustained improvement in constipation appeared to be enhanced by the subsequent infusion of a fecal enema hinting again at

the possibility that an unfavourable composition of colonic flora may have been responsible for the constipation in the first place[12]. In addition to diarrhoea and constipation, some of our patients also developed abdominal pain and bloating although the frequency of these was no different compared to controls.

In this group of 200 patients who were given antibiotics, 16.5% (33) reported one or more symptoms. Those reporting two or more symptoms made up 7.0% (14) and 4.5% (9) met Rome II criteria of IBS. The use of antibiotics has been suggested as a possible pathogenic factor in IBS, possibly via an effect on the bowel flora[5-7]. The association between antibiotic use and IBS needs confirming in longer-term prospective studies. If proved to be a causal relation, then there would be important implications for prescribing, given the economic impact among IBS sufferers. Patients afflicted with IBS have lower work productivity, poorer quality of life, higher healthcare utilisation and healthcare costs[13-20].

Research over the past two decades has provided evidence that administration of probiotics could be used to optimise gut flora and to prevent and treat a range of diseases. Probiotics are defined as live micro-organisms which when administered in adequate amounts confer a health benefit on the host. Bifidobacteria and lactobacilli are commonly used as probiotics. Consumption of specific strains of probiotics is associated with a range of beneficial health benefits in functional bowel disorders such as irritable bowel syndrome and diarrhoeal diseases such as acute infantile diarrhoea, antibiotic associated diarrhoea, and nosocomial infections[21-29]. The impact of probiotics on the antibiotic associated symptoms described in this paper could be the subject of a future study

The clinical contributions of this study is the finding that hard stools can result from antibiotic use in 8.5% of patients and that 4.5% of patients had symptoms that met the ROME II criteria of irritable bowel syndrome. The frequency of antibiotic associated diarrhoea in this study was 11.5%. In the literature review, the range was between 5 to 30%[1-3].

CONCLUSIONS

Patients who were given a course of antibiotics had increased risk of developing bowel disturbances as compared to patients who were not given antibiotics. Patients could develop antibiotic associated constipation rather than diarrhoea. Furthermore, some patients developed symptoms consistent with irritable bowel syndrome (IBS). Further longitudinal study is needed to confirm the association of IBS with antibiotic use.

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