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Original article

Post-infectious irritable bowel syndrome: Role of metronidazole

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SUMMARY

Background: Post-infectious irritable bowel syndrome (PIIBS) represents a subset of patients with irritable bowel syndrome (IBS) whose chronic symptoms follow a documented or presumed bout of acute gastroenteritis. We have observed that patients with IBS often have relief of symptoms when they receive metronidazole on presentation with diarrhoea. Aims: To determine the incidence of PIIBS, and to compare the pattern of rectal inflammation and response to metronidazole in these patients with those in patients with IBS who had no preceding gastroenteritis. Methods: Consecutive patients with IBS (Rome II criteria) who presented to our outpatient department during the period June 2003 to August 2004 were divided into three groups: PIIBS (n=17, 12 men; age 18-60 years), diarrhoea-predominant IBS (IBS-d) (n=35, 29 men; age 19-60 y) and constipation-predominant IBS (IBS-c) (n=24, 18 men; age 18-32 y). Disease characteristics, rectal histology at sigmoidoscopy, and symptom assessment were done at baseline. All patients then received oral metronidazole 400 mg thrice daily for 7 days. Symptoms were reassessed at day 7 (end of treatment) and at day 28 (after 21 days of drug-free period).Results: PIIBS accounted for 18.4% of patients with IBS; all presented with diarrhoea. There was no difference in age at presentation, baseline laboratory parameters, and pattern of rectal inflammation (on qualitative and quantitative examination) in the three groups. Treatment response in the PIIBS and non-PIIBS groups was not different except for stool scores, which improved in the PIIBS group. On subgroup analysis PIIBS and IBS-d groups showed better total score and pain response than IBS-c ($p<0.05$). Conclusions: PIIBS is a diarrhoea-predominant subset of IBS accounting for 18.4% of our outpatient population of IBS. Symptomatic response to metronidazole was better in PIIBS and IBS-d compared to IBS-c.

Key words: Diarrhoea, rectal inflammation

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INTRODUCTION

Post-infectious irritable bowel syndrome (PIIBS) accounts for 6%-17% of patients with IBS.[1] It represents a relatively homogeneous subgroup within the heterogeneous group of IBS, who describe onset of chronic IBS symptoms after an attack of acute gastroenteritis. Earlier studies had shown a better prognosis in these patients,[2] which was not confirmed in subsequent studies.[3]

Antibiotics have shown promising results in subgroups of patients with IBS.[4,5] Metronidazole is frequently used in community practice in India to treat episodes of diarrhoea in patients with IBS. This is done with a presumptive (and erroneous) diagnosis of "chronic amoebiasis". Most patients report relief of symptoms in the short term with this drug. Earlier studies from India[5] had investigated this observation, before the entity of PIIBS gained recognition.

This study was undertaken to study the incidence and epidemiological pattern of PIIBS and to assess the effect of metronidazole in PIIBS compared to the other IBS subgroups.

METHODS

From June 2003 to August 2004 consecutive patients with symptoms of functional bowel disease fulfilling the Rome II criteria[6] for IBS were included in the study if they had none of the exclusion criteria. The latter includ-

ed: age less than 18 years or more than 60 years; history, examination or investigations findings suggestive of organic disease; previous gastrointestinal surgery; concurrent medications that can affect gastrointestinal motility; pregnancy.

All patients were asked about any earlier episode of gastroenteritis or dysentery to which they attribute the onset of their symptoms; in its presence, they were labeled as having PIIBS. The control group comprised patients with IBS and no history of preceding gastroenteritis; they were divided into subgroups with diarrhoea-predominant (IBS-d) or constipation-predominant (IBS-c) IBS. All patients underwent clinical examination and baseline complete haemogram, stool routine and microscopic examination on three consecutive days, and stool culture. Rigid sigmoidoscopy was done and rectal biopsy was taken with punch biopsy forceps (cup diameter 5 mm) in those who consented.

Sections (3 μm) were cut and stained with haematoxylin and eosin (H & E) for morphological and quantitative study. Toluidine blue staining was done for demonstration of mast cells. Well-oriented sections with longitudinal crypt profile were selected for study. Edge areas, traumatic areas and lymphatic follicles were excluded from the study. High-power field was defined at 400X magnification. Five contiguous non-overlapping fields were examined for quantification by a single blinded observer.

Both the groups were given metronidazole 400 mg orally thrice daily for 7 days. Symptomatic evaluation was done using a symptom questionnaire described by Cook et al.[7] This was modified for stool frequency and consistency scores (i.e., normal stool frequency and consistency was given 0 point, and scores were given for both increased or decreased frequency and more hard and liquid stools); the original criteria had scores only for hard stools and decreased frequency. Symptomatic evaluation was done at baseline, on day 7 (end of treatment) and after 3 weeks of drug-free period.

Statistics

Patient characteristics and symptom scores are described using summary statistics. Quantitative variables are summarized using counts (n), means and standard deviations (SD). Qualitative variables are described using frequencies (n) and percentages. Comparison of data was done using Student's 't' test and ANOVA for quantitative and chi-square test for qualitative data; p value less than 0.05 was considered significant.

RESULTS

Two hundred and twenty-four patients with functional bowel disease (Rome II criteria) presented to our outpatient department during the study period. The dominant symptoms were diarrhoea (72), constipation (73), incomplete evacuation (111), and mucus in stools (76). Ninety-two of these (41.1%) had IBS by the Rome II criteria. Seventeen (18.4%) of these patients attributed the onset of their symptoms to a preceding episode of gastroenteritis.

Sixteen of these 92 patients could not be enrolled for the following reasons: stool examination showed parasitic infestation (6), stool culture showed pathogenic growth (1), steatorrhoea (1), diabetes mellitus (2), intake of β-blockers (4), microscopic colitis (1), history of allergy to metronidazole (1). The other 76 patients were classified as patients with symptoms of preceding gastroenteritis (PI-IBS, 17 patients), and those with no preceding history of infection. The latter were subdivided according to their dominant symptoms as diarrhoea-predominant IBS (IBS-d, 35 patients) or constipation-predominant IBS (IBS-c, 24 patients) (Table 1).

Men outnumbered women in all groups. There was no difference in age at presentation between the three groups. Duration of symptoms was significantly longer in IBS-c. Pain scores in the IBS-c and stool scores in the other two groups were significantly higher. Quantitative examination of rectal biopsy showed more mast cells in PIIBS and IBS-c.

Response to treatment

PIIBS: All 17 patients had diarrhoea-predominant IBS. Treatment with metronidazole resulted in significant improvement in pain, stool and total scores at days 7 and 28 compared to baseline. During day 7 to day 28, the drug-free period, the stool symptoms continued to improve ($p<0.05$), but the pain and total scores tended towards baseline. Three of 8 patients with mucus in stool reported improvement that was sustained at day 28.

IBS-d: Treatment with metronidazole resulted in significant improvement in pain, stool and total scores at days 7 and 28 compared to baseline. The stool scores remained persistently low but the pain and total score tended towards baseline. Four patients were lost to follow up after day 7. Ten of 17 (59.1%) noticed improvement in mucus content of stool, which was sustained at day 28 in 7 patients.

IBS-c: There was significant improvement in stool and total scores at day 7 after treatment compared to baseline, but this did not remain significant at day 28. Pain scores did not respond to treatment. Three patients were lost to

Table 1. Patient characteristics at baseline

	IBS-c (n=24)	IBS-d (n=35)	PIIBS (n=17)	P value
Age (years)	33.8 (8.8)	36.7 (10.1)	34.4 (9.1)	
Sex (M:F)	3:1	29:6	12:5	
Duration of symptoms (months)	47.6 (33.2)	33.3 (27.3)	22.2 (17.2)	0.01
Upper GI symptoms (%)	16 (66.6%)	24 (68%)	14 (82.3%)	
Pain score	10.3 (1.3)	9.2 (1.3)	9.4 (1.7)	0.007
Stool score	1.8 (0.6)	3.4 (0.9)	3.8 (0.8)	0.001
Total score	15.4 (1.8)	14.5 (2.6)	15.4 (2.4)	
Mucus in stools	48.5%	58.3%	47.5%	
Rectal biopsy	18 (75%)	31(88.5%)	14 (82%)	
Mast cells/hpf	1.4 (0.9)	3 (1.7)	2.4 (1.2)	0.0002
Mononuclear cells/hpf	109 (28.1)	119.8 (33.9)	111.3 (35)	
IEL/hpf	3 (1.41)	2.2 (1.3)	2.3 (1.2)	

(Data as mean and SD or number and percentage)

follow up after day 7. Eight of 14 patients who complained of mucus in stool showed improvement with treatment, which was persistent at day 28.

When the non-PIIBS groups were combined, they showed similar treatment response, except for stool score, which showed sustained improvement only in the PIIBS group (Table 2). On subgroup analysis the PIIBS and IBS-d groups showed similar response, which was significantly better than IBS-c for pain and total score. The three groups showed similar improvement in mucus content.

One patient each with IBS-d and IBS-c needed discontinuation of treatment due to upper gastrointestinal symptoms, which was reversible on discontinuation of treatment. No patient had allergy or any severe adverse event needing treatment.

DISCUSSION

The Rome II criteria have been considered restrictive in practice but preferable for the purpose of clinical trials, as they provide a more uniform patient population.[8,9] Contrary to the known female predominance among Western patients with IBS, our study population was predominantly male, which is similar to earlier observations from this region.[10] This gender difference in complainants may be due to socio-cultural factors in our society.

We observed several similarities between the PIIBS and IBS-d groups. It is possible that we underestimated the true prevalence of PIIBS because of forgotten or subclinical infections that are common in our country.

The duration of symptoms was similar in the PIIBS and IBS-d groups but was significantly less compared to the IBS-c group. This may represent a favorable prognosis or more severe symptoms in the former two groups. Studies so far, however, do not indicate a better outcome in any of the subgroups.[11]

Different patterns of mucosal inflammation have been reported in different IBS subtypes.[12,13] Rectal histology was qualitatively similar in our groups. Quantitative study, however, showed more mast cells in the IBS-c and PIIBS groups. O'Sullivan *et al*[14] found more mast cells in the caecum in IBS; at other sites the pattern and grade of inflammation was similar. Our patients may have low levels of inflammation resulting from recurrent or subclinical infections that are common in our country. Also, rectal biopsy may not be representative of the whole gut, and changes in the mucosa may not correlate with those in deeper layers. Biopsies from all over the colon, deeper biopsies, and

Table 2. Intergroup comparison of response in total scores to metronidazole (baseline to day 28)

	Total symptom scores			p values			
Period	IBS-d	PIIBS	IBS-c	PIIBS vs. IBS-d	PIIBS vs. IBS-c	PIIBS vs. (IBS-c + IBS-d)	IBS-c vs. IBS-d
Day 0	14.50 (3.1)	15.47 (2.87)	15.44 (2.31)	0.2866	0.9707	0.6919	0.2769
Day 7	9.38 (4.04)	9.71 (4.65)	13.06 (4.57)	0.7986	0.0415	0.2877	0.005
Day 28	10.31 (3.6)	10.33 (5.02)	14.20 (3.28)	0.9851	0.0122	0.1246	0.0005

Values are mean (SD)

immunohistochemistry for differentiating enterochromaffin cells and T-lymphocyte subpopulations may result in better characterisation of inflammation.

Patients with PIIBS and IBS-d had similar response to metronidazole, but those with IBS-c responded less. Similar response to metronidazole was reported earlier from our department[5] in an IBS cohort, but that study did not evaluate effect in subgroups of IBS. At the time of that study, the entity of PIIBS was not well characterised. Pimental *et al*[4] observed significant response to neomycin in IBS. Metronidazole is a cheaper and effective antibacterial alternative that may be evaluated in selected subgroups of IBS, although its safety in the long term should be considered before it can be recommended for clinical use. Pimental *et al*[4] and others[15] used positive breath test as an indication for antibiotic therapy in patients with IBS. Jejunal aspiration is considered the gold standard to document bacterial overgrowth. These procedures have limitations of availability and cost.

In conclusion, post-infectious IBS represents a diarrhoeal subset of IBS and accounts for 18.4% of IBS patients in our outpatient population. There was no difference in baseline laboratory parameters and rectal histology among the different IBS subgroups. Metronidazole therapy resulted in sustained improvement in pain, stool and total score in PIIBS and diarrhoea-predominant IBS subgroups. Stool consistency and frequency improved better than other parameters. Patients with constipation-predominant IBS responded less well to metronidazole.

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