Rifaximin improves symptoms of acquired uncomplicated diverticular disease of the colon

Abstract  Background and aims: We examined the efficacy of cyclic long-term administration of rifaximin, a broad spectrum, poorly absorbable antibiotic, in obtaining symptom relief in a large series of patients with uncomplicated diverticular disease, and compared the incidence of episodes of diverticulitis in the group treated with rifaximin to that in a group receiving fiber supplementation only.  Patients and methods: In a multicenter, prospective, open trial, 968 outpatients with uncomplicated symptomatic diverticular disease were randomized to either fiber supplementation with 4 g/day glucomannan plus 400 mg rifaximin twice daily for 7 days every month (n=558) or 4 g/day glucomannan alone (n=346). Clinical evaluation was performed on admission and at 4-month intervals for 12 months.  Results: After 12 months the group treated with glucomannan + rifaximin showed fewer symptoms (abdominal pain/discomfort, bloating, tenesmus, diarrhea, abdominal tenderness) and a lower global symptomatic score. Overall 56.5% of the patients treated with glucomannan + rifaximin and 29.2% of those treated with glucomannan alone were asymptomatic at 12 months (P<0.001). The rate of complications (diverticulitis and rectal bleeding) was 1.34% in the rifaximin + glucomannan group and 3.22% in the glucomannan alone group (P<0.05).  Conclusion: Cyclic administration of rifaximin is effective in obtaining symptom relief in uncomplicated diverticular disease of the colon. The incidence of episodes of diverticulitis in the group treated with rifaximin was lower than that in the group treated with glucomannan alone.  Keywords  Diverticular disease · Dietary fiber · Glucomannan · Antibiotics · Rifaximin

Introduction  Acquired diverticular disease of the colon is extremely common in the economically developed Western countries [1, 2, 3]. Its incidence increases with age, and while it is uncommon before the age of 40 years, it is estimated to occur in about one-third of all persons over 45 years of age, and in two-thirds of all those over 85 years [4, 5, 6]. In the majority of patients colonic diverticula are asymptomatic (diverticolosis), and only 20% of affected individuals develop symptoms, the condition termed diverticular disease, which may be symptomatic uncomplicated, recurrent symptomatic, or complicated [6, 7, 8]. Additional inflammation involving the bowel wall leads to a condition termed uncomplicated acute diverticulitis. Some authors emphasize that clinical diverticulitis virtually always represents a microperforation, demonstrating that in acute diverticulitis the colonic mucosa is macro- and microscopically normal, despite considerable inflammation of the pericolonic tissue [9]. The presence of free perforation, fistula, abscess or obstruction is termed complicated acute diverticulitis. Lower gastrointestinal
tract bleeding from diverticula is not associated with underlying acute inflammation; rather, the presumed cause of this complication is erosion of a submucosal blood vessel by impacted stool at the neck of a diverticulum.

Diverticulosis has been described as “a disease of western civilization,” in contrast to its rarity in many developing countries [10, 11]. Geographic correlations and time trend analyses suggest that the condition is caused by reduced intake of dietary fiber [10, 11], a hypothesis supported by experimental [12, 13], epidemiological [14, 15, 16, 17, 18], and therapeutic studies [19, 20, 21]. Although the fiber-deficiency hypothesis has been widely quoted, there are still conflicting findings and criticisms [22, 23, 24, 25, 26].

Treatment of diverticular disease is aimed at the relief of symptoms and at preventing major complications [5, 6, 27]. Although the efficacy of a high-fiber diet in managing uncomplicated diverticulitis is still controversial, bran and bulking agents are commonly used. Antispasmodics are also widely used in this condition, although their efficacy has never been clearly demonstrated. Antibiotics are commonly used in the treatment of diverticulitis. Variations in the management of uncomplicated diverticulitis have recently been reported, especially in terms of antibiotic choice, discharge instructions, and follow-up outpatient studies [28]. In uncomplicated diverticulitis, when an inflammatory process is excluded, there is no apparent rationale for using antibiotics. It has recently been reported that cyclic administration of rifaximin (a broad-spectrum, poorly absorbable antibiotic) offers some advantage in obtaining symptomatic relief in uncomplicated diverticulitis over fiber supplementation alone [29, 30]. The rationale for the use of antibiotic in such a subset of patients is the possible role of intestinal microflora in determining some symptoms of uncomplicated diverticular disease by fiber degradation and gas production [31].

The primary goal of the present study was to evaluate the efficacy of cyclic long-term administration of rifaximin in obtaining symptom relief (reduction at 12 months both of the frequency of symptoms and global symptomatic score) in a large series of patients with uncomplicated diverticulitis. Assessment at 12 months both of the frequency rate of symptoms and of the global symptomatic score allowed us to evaluate the efficacy of rifaximin on each individual symptom as well as on the overall severity of the combined symptoms. The secondary goal was to evaluate the incidence of episodes of diverticulitis in the two treatment groups and in particular in the group treated with rifaximin compared to that receiving fiber supplementation only.

Materials and methods

Study design

The study was a multicenter, prospective, randomized, open, controlled trial. Its principal goal was to evaluate the efficacy of rifaximin in obtaining symptomatic relief at 12 months, evaluated by either the frequency of symptoms or the global symptomatic score in patients with uncomplicated diverticular disease. The frequency rate of each individual symptom was evaluated to determine which symptom benefited most from rifaximin. The global symptomatic score was assessed to evaluate the efficacy of rifaximin on the overall severity of the combined symptoms. A secondary goal was to compare the frequency of diverticulitis in the rifaximin group to that in the group receiving fiber supplementation only. The established follow-up period was 12 months. Informed consent was obtained from each patient. The study protocol was approved by the local ethics committee.

Patients

Over a period of 3 years a total of 1030 consecutive outpatients with symptomatic uncomplicated diverticular disease of the colon were screened at 16 Italian cooperative centers. Three main criteria had to be fulfilled to enter the trial: age between 40 and 80 years, endoscopic or radiological evidence of diverticular disease of the sigmoid and/or descending colon, and the presence of troublesome symptoms attributable to the diverticular disease of the colon such as upper and/or lower abdominal pain/discomfort, bloating, tenesmus, diarrhea, and abdominal tenderness. Only patients who had continuously had three or more of these symptoms for at least 1 month (immediately before the trial) entered in the study. Symptoms were graded as mild, moderate, and severe as defined below.

Exclusion criteria were: solitary diverticulum of the colon, signs of diverticulitis, previous colonic surgery, concomitant colonic or extracolonic cancer, use of antibiotics in the previous 4 weeks, hematological disease, immunodeficiency, pregnancy, questionable ability to cooperate, and inability to give informed consent according to the Helsinki Declaration. Diverticulitis was excluded on the basis of clinical and laboratory signs (absence of rebound tenderness or other signs of peritoneal inflammation, and normal values of body temperature, leukocyte, and erythrocyte sedimentation rate) with radiographic or endoscopic examinations (plain abdominal film, barium enema or colonoscopy, ultrasonography or computed tomography, specifically performed on the basis of clinical findings) excluding local inflammatory process of the colonic wall, perforation, abscesses or stenosis [6, 8].

Of the 1030 patients screened 30 were not enrolled because of either inclusion or exclusion criteria, and 32 refused participation. Thus 968 patients entered the study: 595 in the group receiving rifaximin plus glucomannan and 373 in the group receiving only glucomannan. Table 1 presents the demographic and clinical characteristics of the two groups; the groups were homogeneous for age, gender, frequency of symptoms, and mean global symptomatic score. Laboratory values were within the normal range in both groups. Of the 968 patients who entered the study 64 withdrew (37 from the rifaximin group and 27 from the glucomannan group) either as drop-outs or because they developed side effects and