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Metronidazole in the Treatment of Chronic Radiation Proctitis: Clinical Trial

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Aim. To evaluate the effectiveness of metronidazole in combination with corticosteroids in enema and mesalazine (5-aminosalicylic acid) in comparison with the same protocol without metronidazole in the treatment of chronic radiation proctitis.

Methods. Sixty patients with rectal bleeding and diarrhea were randomly divided into two groups. Patients in the first group were treated with metronidazole (3x400 mg orally per day), mesalazine (3x1 g orally per day), and betamethasone enema (once a day during 4 weeks). Patients in the second group were treated with mesalazine and betamethasone enema, but without metronidazole. The efficacy of metronidazole was assessed on the basis of rectal bleeding, diarrhea, and rectosigmoidoscopy findings in all patients.

Results. The incidence of rectal bleeding and mucosal ulcers was significantly lower in the metronidazole group, 4 weeks (p=0.009), 3 months (p=0.031), and 12 months (p=0.029) after therapy. There was also a significant decrease in diarrhea and edema in the metronidazole group, 4 weeks (p=0.044), 3 months (p=0.045), and 12 months (p=0.034) after treatment.

Conclusion. Metronidazole in combination with mesalazine and betamethasone enemas successfully treats rectal bleeding and diarrhea in chronic radiation proctitis.

Key words: *betamethasone enema; diarrhea; flubenisolone; mesalazine; metronidazole; oncology, radiation; proctitis; prostatic neoplasms; radiation effects; radiotherapy*

Irradiation therapy is an accepted method in the treatment of abdominal and pelvic, especially gynecological and urological malignant disease. Radiation induced proctitis is a frequent consequence of external radiotherapy for prostatic carcinoma. The symptoms include diarrhea, rectal bleeding, and pain, which develop after a latency of several weeks, months, or many years following the radiation therapy (1,2). The prevalence of radiation-induced proctitis due to prostatic carcinoma treatment varies from 2% to 20% (3). Total doses of irradiation to the prostate up to 70 Gy were associated with a significant increase in the incidence of radiation proctitis (4).

Traditionally, a variety of treatment modalities have been tried for radiation-induced proctitis, with variable and inconsistent success (5). These include anti-inflammatory agents (6), topical steroid solutions (7), bipolar electrocoagulation (8), hyperbaric oxygen (9), laser application (10), formalin-soaked gauze (11,12), and short-chain fatty acids enema (13). The aim of this study was to evaluate the effectiveness of metronidazole in combination with corticosteroids in enema and peroral mesalazine 5-aminosalicylic acid in the therapy of chronic radiation proctitis.

Patients and Methods

Patients

Sixty patients with chronic radiation proctitis and cytologically proven prostatic carcinoma staged according to the TNM classification from the UICC 1978 (14) as T2N0M0 stage, were assigned to receive either a combination of metronidazole, mesalazine, and corticosteroids in enema, or mesalazine and corticosteroids without metronidazole. Patients were allocated into 2 groups according to the date on which their treatment began: those starting the treatment on even dates were included in the first group, whereas those starting the treatment on odd dates were included in the second group.

The study, approved by the Hospital ethical committee, began in October 1990. The last patient was accrued in October 1997. The patient's characteristics are shown in Table 1. All the patients had histologically approved chronic radiation

Table 1. Characteristics (median, range) and treatment details in patients with chronic radiation proctitis[a]

Parameter	Treatment with	
	mesalazine and betamethasone (control group)	mesalazine, betamethasone, and metronidazole
Age (years)	66 (64–76)	68 (62-74)
Treatment time (weeks)	5.8 (5.2-6.3)	6.0 (5.5–6.5)

[a]Total radiation dose was 68 Gy.

proctitis and gave informed consent to the study. No patients required blood transfusion before treatment.

Cancer Diagnosis and Treatment

Prostatic carcinoma was diagnosed by digital examination, rectal ultrasound, cytological punction, and the prostate specific antigen (PSA) test. The stage of the tumor was determined first by digital rectal examination and then by a CT scan.

All patients were irradiated with linear accelerator using an 8 MV photon beams. The treatment schedule was 5 fractions per week with a daily dose of 2.0 Gy for a mean total dose of 68 Gy in overall treatment time from 5.5 to 6.5 weeks. The mean frontal field size was 12x12 cm, and the mean lateral field size 10x16 cm. The irradiation was performed in a 3-field technique and a shrinkage field was used in all patients after 50 Gy with a field size of 9x9 cm. There was no difference in the radiotherapy between the two treatment arms.

Median interval from the last radiation dose to the study was 12.2 months (range 10 to 16 months).

Diagnostic Criteria of Chronic Radiation Proctitis

All patients underwent a complete patient history examination and laboratory analysis (red blood cell count, white blood cell count, urine, aspartate amino-transferase, alanine amino-transferase, coagulation tests, creatinine), stool examination (culture for *Clostridium difficile, Staphylococcus, Campylobacter, Salmonella, Shigella,* and examination for ova and parasites), digital examination, anoscopy, rectosigmoidoscopy, contrast study of the small bowel, barium enema, and endoanal ultrasound. Each of the patients suffered from chronic symptoms (rectal bleeding and diarrhea). Apart from secondary anemia, all other laboratory tests results were within the normal range. Anoscopy showed mucosal hyperemia, edema, small ulcerations, and blood and slime in the anal canal. Rectosigmoidoscopy revealed intense erythema, edema, friability, ulcerations, and teleangiectasia up to 10 cm from the anal verge. Changes were more intense on the anterior wall of the rectum. In all cases, the diagnosis was established by histological examination of the rectal mucosa, which showed an ischemia caused by obliterative endarteritis and fibrosis (1), although most authors rarely consider biopsy of rectum an acceptable method, since it may precipitate ulceration and fistula formation (15).

Treatment of Chronic Radiation Proctitis

Patients in the metronidazole group were treated with metronidazole (*Medazol*, Belupo, Koprivnica, Croatia) 3x400 mg orally per day, mesalazine (5-aminosalicylic acid; *Salofalk*, Dr. Falk Pharma, Freiburg, Germany) 3x1 g orally per day, and betamethasone enema (*Betnesol*, Glaxo-Wellcome, Hamburg, Germany) once a day during 4 weeks. The group without metronidazole was treated with mesalazine and betamethasone enema the same way as the first group during 4 weeks.

Assessment of the Proctitis

All patients were given a calendar and instructed to record every change connected with medications they took, details of bowel action (number of bowel movements, amount and frequency of hematochezia), and usage of any other medication in addition to the drugs under investigation. Objective patient response was documented by rectal bleeding score (Table 2) and diarrhea score (16). The patients were scored the same way before and after treatment. The same physician interviewed patients once a week during the treatment period. After 4 weeks of treatment, the therapy was discontinued. During the first year, the patients were reexamined for recurrence of symptoms every 3 months. After that period, control examination was performed every 6 months. Adverse reactions (skin rash, nausea, or vomiting) that occurred during the treatment were considered treatment toxicity. Reappearance of symptoms in patients who were symptom-free for at least 3 months after treatment was considered a recurrence and the same therapy was reapplied for an additional 4-week period.

Table 2. Assessment score for diarrhea and rectal bleeding

Score	Parameter	
	Diarrhea	Rectal bleeding
0	no change in bowel habits (normal)	no blood in stool
1	small increase in frequency; soft stools	stool covered with blood
2	more pronounced increase in frequency; loose stools	stool mixed with blood
3	considerable increase in frequency and watery stools	only blood

Persistence of any symptom 4 weeks after the beginning of therapy was considered a therapy failure, and the therapy was discontinued. The longest follow-up period after 4 weeks treatment was 3 years, whereas the shortest one was 2 years.

Statistical Analysis

Differences in categorical variables between groups were tested with Fisher's exact test.

Results

None of the patients were excluded due to the intolerance of therapy or adverse reactions to the medications. At the beginning of treatment and during the control examination period, none of the 60 patients was positive for *Clostridium difficile, Staphylococcus, Campylobacter, Salmonella, Shigella*, ova, or parasites. Barium enema and small bowel follow-through contrast study did not show changes in other parts of large and/or small intestine. Endoanal ultrasound did not show the damage of the internal anal sphincter.

Rectal Bleeding

After 4 weeks of the treatment, there was a statistically significant difference in the occurrence of rectal bleeding between the group with metronidazole and group without metronidazole (Table 3). Similar results were observed 3 and 12 months after the cessation of metronidazole therapy (Table 4). Two years after the treatment, the incidence of rectal bleeding was similar in both groups.

Diarrhea

A statistically significant difference in the occurrence of diarrhea between group with metronidazole and group without metronidazole was also documented after 4 weeks of treatment (Table 3). Similarly, decrease in the incidence and severity of diarrhea was observed after 3 and 12 months

Table 3. Incidence and severity of diarrhea, rectal bleeding, and endoscopy findings before and four weeks after therapy in patients with chronic radiation proctitis[a]

Parametar		Before			After 4 weeks		
		metronidazole	control	p	metronidazole	control	p
Symptom score:							
rectal bleeding	0-1	0	0	N.T.[b]	27	18	0.009
	2-3	30	30		3	12	
diarrhea	0-1	15	13	0.617	29	24	0.044
	2-3	15	17		1	6	
Rectosigmoidoscopy for rectal mucosa:							
no erythema/erythema		15/15	13/17	0.617	29/1	24/6	0.044
no ulcers/ulcers		0/30	0/30	N.T.	27/3	18/12	0.009
no teleangiectasia/teleangiectasia		0/30	0/30	N.T.	0/30	0/30	N.T.

[a]Patients in the metronidazole group (n=30) were treated with metronidazole, mesalazine and betamethasone enema and those in the control group (n=30) with mesalazine and betamethasone.
[b]Not tested.

in both groups (Table 4). After 24 months of treatment, no statistically significant difference in the occurrence of diarrhea between the group treated with metronidazole and the control group without metronidazole was found.

Rectosigmoidoscopy

The incidence of mucosal ulcers was significantly lower in the group treated with metronidazole than in the group without metronidazole treatment 4 weeks after treatment (Table 3). Similar results were observed after 3 and 12 months of treatment (Table 4).

After 4 weeks of treatment, there was a statistically significant difference in the occurrence of the erythema/edema between the group treated with metronidazole and the group without metronidazole treatment (Table 3). Similar results were observed after 3 and 12 months of therapy (Table 4).

After 24 months of treatment, there was no statistically significant difference in the occurrence of mucosal ulcers and erythema/edema between the two groups (Table 4).

Teleangiectasiae were found in all patients from both groups. After the treatment, there was no difference in incidence of teleangiectasia in both groups. We observed prolonged healing and long-lasting ulcer on the site of biopsy in all patients, and did not perform biopsies at control rectosigmoidoscopies.

Discussion

In our patient series, the use of metronidazole in combination with mesalazine and corticosteroid enemas in the treatment of radiation proctitis significantly decreased rectal bleeding and mucosal ulcerations, as assessed by rectosigmoidoscopy.

This finding is significant because rectal bleeding, most often caused by ulcerations of rectal mucosa (2), was the worst symptom in our patients with chronic radiation proctitis. Various therapeutic approaches to these symptoms were proposed: sulfasalazine and oral corticosteroids (17), corticosteroid enemas (7), bipolar electrocoagulation (8), tranexamic acid (18), endoluminal formalin (11,12), and more recently, hyperbaric oxygenation (9), or laser therapy (10). The cases of massive rectal

Table 4. Incidence and severity of diarrhea, rectal bleeding, and endoscopy findings 3 months, and 1 and 2 years after therapy in patients with chronic radiation proctitis[a]

Parametar		After 3 months			After 1 year			After 2 years		
		metronidazole (n=27)	control (n=18)	p	metronidazole (n=24)	control (n=12)	p	metronidazole (n=19)	control (n=10)	p
Symptom score:										
rectal bleeding	0-1	26	13	0.031	22	7	0.029	18	8	0.267
	2-3	1	5		2	5		1	2	
diarrhea	0-1	25	12	0.045	23	8	0.034	18	7	0.105
	2-3	2	6		1	4		1	3	
Rectosigmoidoscopy for rectal mucosa:										
no erythema/erythema		25/2	12/6	0.045	23/1	8/4	0.034	18/1	7/3	0.105
no ulcers/ulcers		26/1	13/5	0.031	22/2	7/5	0.029	18/1	8/2	0.267
no teleangiectasia/teleangiectasia		0/27	0/18	N.T.[b]	0/24	0/12	N.T.	0/19	0/10	N.T.

[a]Patients in the metronidazole group were treated with metronidazole, mesalazine and betamethasone enema and those in the control group with mesalazine and betamethasone.
[b]Not tested.

bleeding that could not be managed with conservative methods always require surgical therapy (2).

We used metronidazole because of its immunomodulation effects (19) and a selective toxicity to anaerobic or microaerophilic microorganisms that contribute to hypoxia of irradiated rectal tissue (20).

The exact cause of diarrhea during abdominal and pelvic radiotherapy is not known. Although diarrhea usually accompanies rectal mucosal lesion, some authors believe that it is caused by the small intestine radiation injury (1). Since the small bowel follow-through contrast study results were normal in our patients, we excluded radiation enteritis as a cause of diarrhea.

Bile acid malabsorption and bacterial contamination by anaerobic and aerobic bacteria is a common cause of diarrhea after the radiation treatment of gynecological cancer (21). Damage of the pelvic floor and nerves by irradiation may partially explain the experienced urgency of defecation. The physical properties of the rectum, i.e., its compliance and capacity, may also be irreversibly altered (22). Radiotherapy for prostatic cancer also affects the internal anal sphincter causing urgency, increased frequency of defecation, and even incontinence (23,24). In our study, endoanal ultrasound showed that internal anal sphincter was not affected. There are other ways to evaluate anal sphincter functionality, i.e., anal manometry, but for the purpose of this study endoanal ultrasound was sufficient.

Two studies involving patients with chronic radiation proctitis showed that treatment with either sulfasalazine or aspirin was beneficial in improving the symptoms and radiological and proctoscopic signs of proctitis (17,25). Other studies showed that a combination of sulfasalazine with prednisolone (26) and sucralfate in oral form (16) was successful in the treatment of massive diarrhea in radiation proctitis. There was no evidence that the various aminosalicylic acid derivatives and/or corticosteroids given orally or as an enema were beneficial in preventing progressive disease (27). Treatment with nonsteroidal anti-inflammatory agents, misoprostol (a prostaglandin E_1 analogue) or sucralfate did not ameliorate or exacerbate radiation proctitis in rats (28).

Danielsson et al (21) also found significant decline in the frequency of radiotherapy induced diarrhea after treatment with a combination of metronidazole and doxycycline for 7-10 days. In our study, the frequency of diarrhea or the number of defecation episodes, which are probably the most objective parameters, showed a significant downward trend in the metronidazole treatment when compared to the treatment without metronidazole.

Our study also showed that mucosal erythema regressed and mucosal ulcerations healed after metronidazole treatment. Healing of ulcers was also noted by others (29).

Since late radiation proctitis is a result of vascular damage and progressive ischemia of the rectal wall, the usefulness of anti-inflammatory drugs can hardly be expected. So far, most reports could not show local or systemic drug therapy to have any effect on chronic radiation proctitis (6), although there are suggestions that symptoms of radiation induced proctitis are in most cases reversible and susceptible to conservative treatment (2).

Jao and co-workers (2), suggesting an aerobic infection as the underlying cause, succeeded in ameliorating rectal pain with metronidazole treatment. In our study, stool cultures were negative for *Clostridium difficile, Staphylococcus, Campylobacter, Salmonella, Shigella*, ova, or parasites at the beginning and at every controlexamination. This suggests that anaerobic infection may not be present and thus may not be a relevant etiologic factor in the generation of bleeding and diarrhea. Recidives appeared with similar incidence in both groups, 3 months after the end of the therapy, usually as a reappearance of rectal bleeding and diarrhea.

In conclusion, our study showed that metronidazole in combination with mesalazine and betamethasone enema can be beneficial in the treatment of chronic radiation proctitis and especially in relieving the symptoms such as rectal bleeding and diarrhea. The possible mechanism of beneficialeffect of metronidazole treatment could be explained by the selective effect on anoxic or hypoxic cells of rectal mucosa.

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