Effect of Indomethacin Suppositories on Rectal Polyposis in Patients with Familial Adenomatous Polyposis

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BACKGROUND. Oral sulindac is known to reduce polyps in patients with familial adenomatous polyposis (FAP). The authors speculated that rectal administration of indomethacin would be effective therapy for adenomas in the rectal remnant of FAP.

METHODS. Eight patients with FAP who had been treated by total colectomy with ileorectal anastomosis were administered an indomethacin suppository (50 mg) once or twice daily during a period of 4 or 8 weeks. The number of polyps at the same site within the rectum was counted under proctoscopy prior to, at the end of, and after the treatment. In four patients, proliferative activity of the rectal mucosa was assessed by immunohistochemical staining for MIB-1.

RESULTS. In six of the eight patients who initially had ten or more polyps, the number of polyps decreased to fewer than five, whereas such a decrease could not be observed in the remaining two patients. In the six patients, the number of polyps increased after indomethacin was discontinued. The proliferative activity of the rectal mucosa was higher at the end of treatment than it was prior to indomethacin administration.

CONCLUSIONS. Indomethacin suppositories may be effective in the management of rectal adenomatosis in patients with FAP. ***Cancer* 1996; 78:1660–5.**

KEYWORDS: familial adenomatous polyposis, rectum, therapy, indomethacin, sulindac.

Familial adenomatous polyposis (FAP) is a hereditary disease, characterized by multiple adenomatous polyps and a high incidence of associated colorectal carcinomas. Patients with this disease are treated by total colectomy or by proctocolectomy. Although ileal pouch-anal anastomosis has been more frequently used as treatment of the disease in recent years,[1] the rectal remnant should be carefully surveyed for the possible occurrence of cancer in patients who have been treated by total colectomy with ileorectal anastomosis.

It has been reported that sulindac, one of the nonsteroidal antiinflammatory drugs (NSAIDS), causes regression of polyps in patients with FAP.[2] Subsequent investigations confirmed that sulindac[3–7] and indomethacin[8] decrease polyps in patients with FAP, but the polyps recur after discontinuation of the agents. However, in such investigations the NSAIDs mainly were administered orally. It was speculated that rectal administration may be more effective against rectal polyps, especially in those patients whose rectum is under surveillance. Therefore, the short term effect of indomethacin suppositories with

TABLE 1
Characteristics of Patients

Patient no.	Sex	Age (yrs.)		Length of rectal remnant (cm)	Indomethacin	
		Colectomy	Entry		Dose (mg/day)	Duration (wks)
1	M	39	57	8	100	4
2	M	24	26	12	100	4
3	M	24	30	10	50	8
4	F	29	43	15	100	8
5	F	10	26	12	50	4
6	F	28	45	15	100	4
7	M	31	37	10	100	4
8	M	26	34	15	100	4

M: Male; F: female.

respect to endoscopic and immunohistochemical view was investigated.

MATERIALS AND METHODS

This study was conducted on eight patients with the established diagnosis of FAP, who had been treated by total colectomy with ileorectal anastomosis and who had been observed on an outpatient basis at our institution. These patients were free from any disorders other than FAP, such as liver damage and renal insufficiency. Table 1 summarizes the clinical features of the patients. There were 5 males and 3 females, and the age at entry to the trial ranged from 26 to 57 years (mean, 37 years). There were time intervals ranging from 2 to 18 years (mean, 11 years) from the colectomy until this investigation.

After obtaining informed consent from each patient, the subjects underwent proctoscopy prior to the initiation of indomethacin treatment. Thereafter, the patients were administered indomethacin suppositories (Banyu Co., Tokyo, Japan) for either 4 or 8 weeks. Each suppository contained 50 mg of bioactive indomethacin. Six patients received 100 mg of indomethacin twice daily, and the remaining 2 patients were administered 50 mg once daily (Table 1). Thus, the patients were divided into four groups of treatment, according to the dose of indomethacin and the duration of treatment. At the end of the indomethacin treatment, the effect of the indomethacin suppository was assessed by proctoscopy. In 7 of the 8 patients, proctoscopies were performed periodically during the period ranging from 39 to 96 months (mean, 15.6 months) after discontinuance of treatment. Two patients were again administered indomethacin.

Assessment of Rectal Polyps

At the initial examination, the exact site within the rectum was confirmed by measuring the length of the tip of proctoscope from the anal ring. After spraying 0.2% indigo carmine solution, the endoscopic view was recorded on videotape. Exactly the same view within the rectum was obtained during the subsequent proctoscopies.

The number of polyps was counted independently by two colonoscopists, who were blind to the treatment utilized for the patients. The investigators observed all the recorded endoscopic views of the individual proctoscopy, and were instructed to select endoscopic views from each examination that identified the same site within the rectum. The number of any polyps was counted three times per endoscopic view, and the median value was chosen as the number of polyps in each examination. The number of polyps was thereafter graded as follows: Grade 1: 0; Grade 2: 1–4; Grade 3: 5–10; Grade 4: 11–50; and Grade 5: more than 51 per field.

Proliferative Activity of the Rectal Mucosa

Proliferative activity of the rectal mucosa was assessed prior to and at the end of indomethacin treatment, using immunohistochemical staining for MIB-1 antibody.[9]

During the proctoscopy, biopsy specimens were obtained from normal-appearing rectal mucosa. These specimens were fixed in 10% formalin, embedded in paraffin, and cut in sections at 5-μm thickness.

The sections were deparaffinized to distilled water in a xylene and ethyl alcohol series, and kept in methyl alcohol solution with 3% hydrogen peroxide for 30 minutes to block intrinsic peroxidase activity. The sections were rinsed in 0.1 mol/L sodium tetraborate for 1 minute; rinsed 3 times in 0.01 mol/L phosphate-buffered saline (PBS); and 10% rabbit serum then was applied for 10 minutes. After these procedures, the sections were incubated in MIB-1 monoclonal antibody (1:100) (mouse immunoglobulin G [IgG]; Immu-

notech SA, Marseilles, France). After overnight incubation, the sections were rinsed 3 times, for 5 minutes each time, in PBS, and a biotinated second antibody (antimouse IgG, A, and M; Histofine SAB-PO(M) kit; Nichirei, Tokyo, Japan) then was applied for 20 minutes. The subsequent development of antibody-bridge labeling was made by the streptavidin-biotin peroxidase method (Histofine SAB-PO kit) with hematoxylin counterstaining.

Under X400 high-power view, the numbers of MIB-1 positive and negative cells within all the crypts that were cut along their longitudinal axis were counted. The proliferative activity of each specimen was expressed as the labeling index, which was calculated as the percentage of the number of MIB-1 positive cells against the number of all cells counted. At least 300 cells were counted in each specimen.

Statistical Analysis

When comparing the grade in the number of polyps and the proliferative activity of the rectal mucosa between prior to and at the end of indomethacin treatment, Wilcoxon's signed rank test was used for statistical analysis. Probabilities < 0.05 were considered to be significant.

RESULTS

Among the eight patients who participated in this study, seven completed the indomethacin suppository treatment, whereas the remaining patient (Patient 2) could not tolerate the treatment because of tenesmus that occurred immediately after the insertion of the indomethacin suppository.

Changes in the Number of Rectal Polyps

Figure 1 shows serial changes in the grade of number of rectal polyps. Although the grade was 4 or more in all patients, it was significantly decreased at the end of indomethacin treatment ($P < 0.05$). An example of an obvious decrease in the number of polyps is illustrated in Figure 2. In five of the seven patients whose polyposis was regarded as Grade 5 prior to the therapy, the endoscopic grade decreased to either Grade 2 or Grade 1 at the end of treatment. In the other two patients, changes in the endoscopic grade were less than 2. These two patients were treated with 50 mg of indomethacin. One of these patients, in whom regression in the number of polyps was not observed, was the case of tenesmus.

However, after the discontinuance of the indomethacin suppository, the number of rectal polyps gradually increased (Fig. 1). As shown in Figure 1, the increase in the number of polyps even occurred within 4 months after discontinuance of the treatment, and

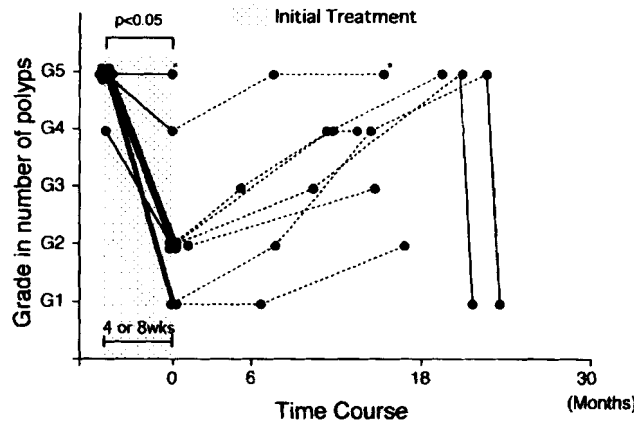

FIGURE 1. Changes in endoscopic grade in number of rectal polyps. Solid lines indicate the period of indomethacin treatment. Dotted lines indicate serial changes after discontinuation of indomethacin. •: patients treated by 50-mg indomethacin. Other patients were administered 100 mg of indomethacin.

recurrence was observed within 15 months in all 6 patients whose grade was decreased by more than 2 by indomethacin. In two patients in whom complete regression and subsequent recurrence of rectal polyps were confirmed, a second administration of an indomethacin suppository for 4 weeks was initiated after 20 and 22 weeks. This second treatment again resulted in a marked decrease in the number of polyps.

Proliferative Activity of the Rectal Mucosa

In six patients, biopsy specimens were obtained both prior to and at the end of indomethacin treatment. However, labeling index for MIB-1 antibody could not be compared between these time points in two patients because the number of crypt cells that could be counted under microscopy was insufficient for the estimation (less than 300).

The labeling index of the rectal mucosa prior to the use of an indomethacin suppository ranged from 0.02 to 0.20. The value at the end of the treatment increased, ranging from 0.09 to 0.23, in all 4 patients in whom the values could be compared (Fig. 3). Although the labeling index showed an obvious increase in 1 patient (from 0.04 to 0.18), there was no such increase in the remaining 3 patients. The difference in labeling index between the two time points did not reach statistic significance ($P = 0.068$).

DISCUSSION

In 1983, Waddell et al.[2] first reported that oral sulindac reduced colorectal adenomas in patients with FAP. The effect of the drug was subsequently confirmed in other investigations,[3–6] and the oral sulindac is now

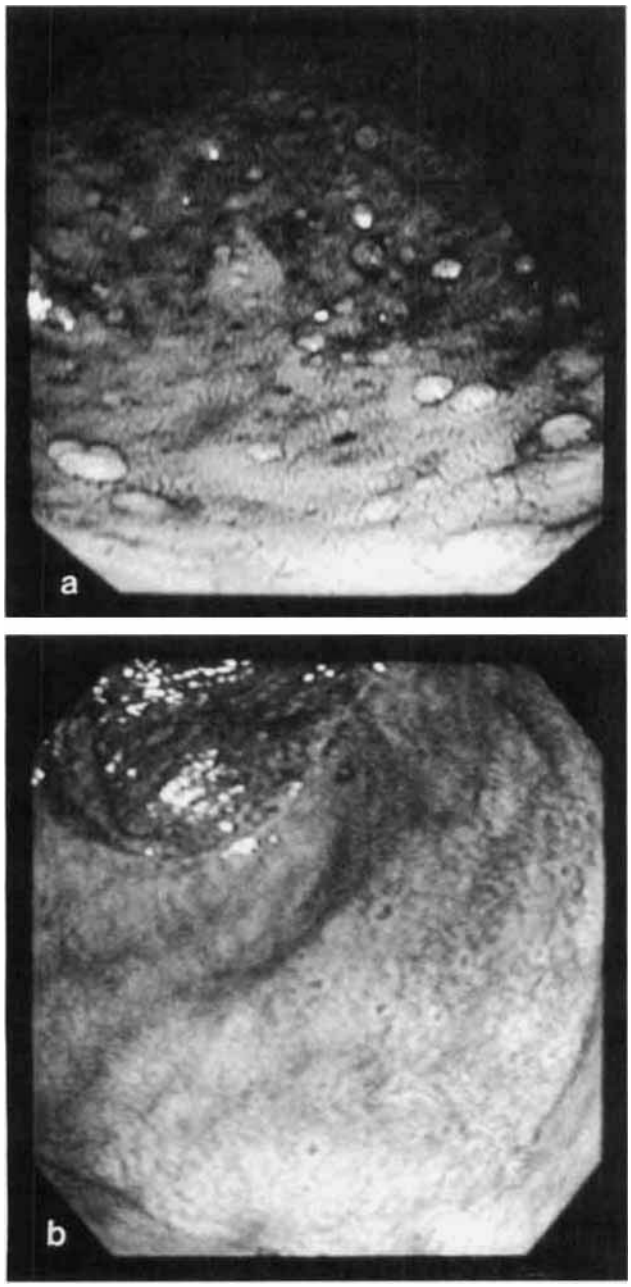

FIGURE 2. An example of regression in rectal polyps (Patient 4). (a) Endoscopic view prior to indomethacin treatment indicated that there are numerous polyps in the rectal remnant. This polyposis is regarded as Grade 5 according to our criteria. (b) At the end of indomethacin treatment for 4 weeks, no polypoid lesion could be identified (Grade 0).

known as a treatment of choice for patients with the disease.

These results indicated that rectal polyps in FAP decreased in number by administering indomethacin intrarectally. There were two previous reports demonstrating the effect of intrarectal NSAIDs on rectal adenomas in FAP.[7,8] In these investigations, either sulindac[7] or indomethacin[8] decreased the number of rectal polyps. In contrast to these reports, Waddell et al.[2] reported that oral indomethacin failed to reduce the number of rectal adenomas. Although the effect of oral indomethacin was not investigated in the current study subjects, indomethacin suppositories were effective both in our study and in two cases reported by Hirata et al.[8] The discrepancy in the effect of indomethacin can be explained by the difference in the concentration of the agent within the rectum, because only 12% of orally administered indomethacin reaches the rectum.[10]

Because sulindac is a long acting analogue of indomethacin, and the agent reveals its bioactive effect after being metabolized by bacterial flora, there remains a possibility that indomethacin and sulindac are different from each other in their ability to cause regression of rectal polyps. However, Winde et al.[7] reported that 6 weeks' treatment using sulindac suppositories resulted in complete or partial regression of rectal polyps in 13 of 15 patients with FAP. This result appears to be similar to that confirmed in the current study. Although we could not determine which of the two suppositories, sulindac or indomethacin, is superior to the other in reducing the number of polyps, indomethacin suppositories may be an alternative method for the management of rectal polyposis in FAP.

Mechanisms by which NSAIDs reduce rectal adenoma have not been clearly understood. An in vitro study[11] suggested that regression of neoplasia by NSAIDs is possibly due to alterations in the cell cycle via suppression of prostaglandin synthesis. This hypothesis apparently explains the results of the current study and other reports with sulindac,[2-7] because both indomethacin and sulindac inhibit cyclooxygenase activity. However, in the current study, the proliferative activity of the rectal mucosa was increased at the end of indomethacin treatment. Because it has been reported that indomethacin increases cell loss and DNA content of the mucosa within the intestinal tract,[12] the increased proliferation of the rectal mucosa observed in the current study may be the result of direct action of indomethacin.

This finding appears to be in contrast with a previous investigation,[6] in which sulindac reduced rectal polyps without any change in the proliferation of the rectal mucosa. The discrepancy in proliferative activity may be explained by the difference in the agent and in the route of administration, because an in vitro study confirmed that sulindac sulfide, a metabolite of sulindac, has strong antiproliferative activity.[13] Because the number of samples in the current study was small,

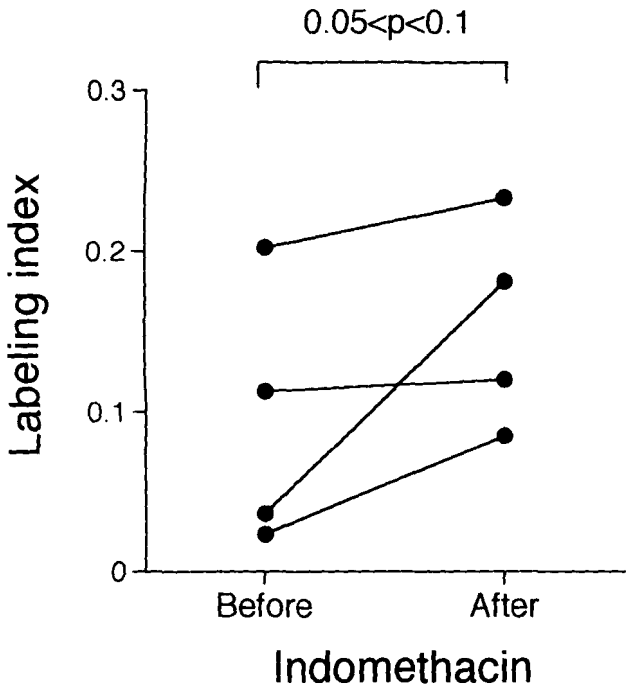

FIGURE 3. Comparison of labeling index of the rectal mucosa.

further studies using other techniques for the assessment of proliferative activity with many more subjects are warranted to draw a reliable conclusion. In any event, because our study and another in vivo investigation[6] failed to identify a decrease in mucosal proliferation, clinical response of rectal polyps to NSAIDs within a short term treatment plan does not appear to be attributed to the suppression of cell proliferation. As confirmed in recent investigations,[13,14] enhanced apoptosis by NSAIDs may play a much more important role in regression of polyps.

Although the number of polyps was actually decreased by use of an indomethacin suppository, it gradually increased within 15 months after discontinuation of the treatment. Similar observations were reported in two investigations,[3,4] in both of which oral sulindac was administered. However, in the current study, a second trial of indomethacin suppositories was effective in two patients. Although the number of subjects in each treatment group was too small to establish a standard method, intermittent application of an indomethacin suppository for 4 weeks should be available for the patients, because regression of the rectal polyposis could be observed within this period of treatment, and indomethacin is reported to be tolerable for many years.[15] Such a strategy should be compared with previously described oral or rectal sulindac use[2-7] to establish the clinical value of indomethacin suppositories.

Experimental and epidemiologic studies[16-19] confirmed the possibility that NSAIDs have chemopreventive action for colorectal carcinomas. However, it still remains unclear whether NSAIDs treatment for FAP actually decreases the incidence of rectal carcinoma in our subjects and in other surveys. In addition, noteworthy cases of FAP in which rectal carcinoma developed after sulindac treatment have been described.[20-22] Thus, further studies regarding the chemopreventive effect of NSAIDs against FAP seem necessary. However, the results of the current study suggest that indomethacin suppositories may be the treatment of choice for patients with FAP after ileorectal anastomosis. The dramatic regression of rectal polyps possibly reduces the necessity of endoscopic or surgical removal during the surveillance of the rectal remnant in patients with this disease.

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