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The NSAID sulindac reverses rectal adenomas in colectomized patients with familial adenomatous polyposis: clinical results of a dose-finding study on rectal sulindac administration*

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Abstract. After colectomy with ileorectal anastomosis (IRA) for treatment of familial adenomatous polyposis (FAP), the rectal mucosa remains, with the risk of malignant change. Locoregional (rectal) sulindac has been applied, with initial higher-dose therapy and subsequent low-dose maintenance therapy to minimise side-effects. The dose-finding study with sulindac suppositories started with a dose of 300 mg sulindac daily per patient over 6 weeks. Depending on proctoscopical evaluation of regression of polyposis, sulindac doses were reduced in predefined steps. Ten of 15 patients developed a complete remission following 42 weeks of treatment, while the rest had partial remission. Responses were recorded 6–24 weeks after beginning sulindac treatment. After 36 weeks, 13/15 patients received 25–50 mg sulindac daily. An increase in the number of partial remissions after 42 weeks of treatment at doses of 100 mg sulindac daily may indicate the first approach to a reduced dose between 100 mg to 25 mg sulindac daily, but may also point to the importance of long-term treatment rather than dose-intense therapy.

Résumé. Après colectomie et anastomose iléo-rectale (AIR) pour le traitement de la polypose adénomateuse familiale (PAF) il demeure un risque de malignisation de la muqueuse rectale. Une application locale (rectale) de Sulindac a été effectuée avec des doses initiales élevées et une poursuite du traitement avec des doses plus faibles afin de diminuer les effets nocifs. L'étude dose-relation avec des suppositoires de Sulindac a commencé avec une dose de 300 mg de Sulindac quotidiens par malade pendant 6 semaines. Selon l'évaluation de la régression des polypes en proctoscopie, les doses de Sulindac étaient réduites de façon prédéfinie. 10 des 15 malades ont développé une rémission complète après 42 semaines de traitement tandis que les autres avaient une rémission partielle. La réponse a été réévaluée 6 à 24 semaines après le début du traitement par Sulindac. Après 36 semaines, 13 des 15 patients avaient reçu 25 à 50 mg quotidiens. L'augmentation du nombre des rémissions partielles après 42 semaines de traitement à la dose de 100 mg de Sulindac quotidiens peut indiquer une première approximation pour des doses réduites entre 100 et 25 mg de Sulindac quotidiens mais peut aussi souligner l'importance du traitement à long terme plutot que de l'intensité des doses thérapeutiques.

Patients with familial adenomatous polyposis (FAP) have a high risk of colorectal cancer but also other tumours [1]. Surgical therapy is the treatment of choice, using proctocolectomy with Brooke's ileostomy, restorative proctocolectomy with ileoanal pouch, or colectomy with ileorectal anastomosis (IRA) [1]. The latter method accounts for more than 80% of all surgical interventions, for it is a simple, low-risk procedure with very good functional outcome [2, 3, 4]. After colectomy with IRA, the risk of adenomatous proliferation in the mucosal remnant remains, with the suggestion that the incidence of dysplasia and carcinoma becomes higher with longer observation periods [4, 5]. Surveillance with proctoscopy and routine polypectomy or fulguration every 3 to 6 months is necessary, depending on the extent of adenoma development [1, 4]. A low-risk, well-tolerated antiproliferative treatment to the rectal mucosa might achieve adenoma regression, perhaps allowing less intense surveillance. Several authors have reported that daily oral administration of 150–400 mg of sulindac, an inhibitor of prostaglandin synthesis with anti-inflammatory and antiproliferative activity [6], leads to eradication of adenomas and micro-adenomas in FAP [7–13].

Therefore, a study with logoregional (rectal) application of sulindac was performed, involving 15 patients after colectomy and IRA in order to investigate the therapeutic effect and side-effects of rectal administration and to define the dose required to maintain adenome suppression.

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Patients and methods

Patients selection and study design. Patients with histologically confirmed FAP, at least 3 years after colectomy with IRA, entered the study. After initial spontaneous adenoma regression after colectomy, all patients developed rectal polyps again. Adenomas of tubular or tubulovillous type, varying in size (maximum 8 mm) and number (5–45) with up to severe dysplasia were confirmed at biopsies. Eligibility requirements included age < 60 years, WHO performance status ≤ 2, adequate bone marrow, liver and renal function, no other gastrointestinal disorders, informed consent. Patients with gastrointestinal disorders other than extracolonic manifestations (ECMs), prior treatment of cancer, pregnancy or lactation were excluded.

It was felt that randomization would be difficult, particularly within families, leading to diminished compliance. Moreover, variability of phenotypic expression would cause difficulties in randomization of relative small groups. Therefore, it was decided to include patients with different degrees of expression of FAP and to use the treatment in all age groups to examine the relative effects of long-term low-dose NSAID treatment.

Control group. Ten patients with histologically confirmed FAP, at least 3 years after colectomy with IRA and meeting the eligibility requirements of the study group served as a non-randomised controlgroup. Routine proctoscopy followed at 3 month intervals with polypectomy or fulguration. The protocol was approved by the local Ethics Committee of the University of Münster.

Pre-treatment follow-up examinations. Prior to entry, patients underwent upper GI-endoscopy, abdominal and thyroid ultrasound scanning, fundoscopic examination, mandibular pantomography, proctoscopy with endoscopic documentation and selective biopsies. Proctoscopy with biopsies and endoscopic photo-documentation were repeated every 6 weeks for the first year of the treatment; after that re-examination was at 12-week intervals. Laboratory work-up with full blood count (differential and platelet count), liver and renal function tests were done before the start of treatment, every six weeks during treatment and every 12 weeks after one year of treatment.

Response and Toxicity. Patients were considered evaluable for response and toxicity if they had received at least six weeks of treatment. Response criteria were classified as follows:

no regression	(NR): unchanged extent of size and number of rectal polyps
progressive disease	(PD): increase in size and number of rectal polyps
clinical incipient regression	(CIR): decrease in size and numbers of polyps
clinical partial regression	(CPR): no evidence of polyps but visible disease (mucosal elevations e.g. nascient or intramucosal adenomas, only histologic work up confirming the diagnosis)
clinical complete remission	(CCR): no visible evidence of disease

Toxicity was evaluated by worst event for each organ system.

Treatment plan. Sulindac was administered as suppositories at a starting dose of 300 mg daily for 6 weeks. Dosage handling depended on the regression of polyps after re-examination every 6 weeks, i.e. a visible improvement compared to the preceding examination was followed by a dose reduction; no regression or progression was followed by termination of the therapy after 6 months at the starting dose level. Worsening of the proctoscopic appearance – reappearance of polyps after complete remission, or increasing numbers after partial regression – was managed by reversion to the preceding higher dose level. It was planned to decrease the sulindac dose in steps from 150 mg to 100 mg, to 75 mg, to 50 mg and to 25 mg twice daily in order to find an approach to the lowest effective dose. No discontinuation of sulindac treatment was planned for responding patients.

Results

Response

The 15 patients included 11 females. The mean age was 33 years and (range 18–53 years). The evaluation was completed when all patients had undergone seven treatments and re-examinations, with intervals of six weeks between. All patients entered the study with visible and/or histologically defined adenomas of varying size and numbers. No progressive disease was documented.

After 6 weeks of treatment at 300 mg/day only 13% ($n = 2$ of 15) of the patients were without response, 1 of 15 patients showed an incipient response (CIR) with visible polyps left, 3 of 15 patients showed a partial response (CPR) and 9 of 15 patients had a complete response (CCR). 12 of 15 patients had dose reductions to 200 mg per day. After 12 weeks of treatment, residual polyps (CIR) were still present in 2 of 15 patients; 67% ($n = 10$ of 15) patients had undergone a complete regression of polyps.

After 18 weeks of treatment, there was still 1 of 15 patients with visible disease (CIR) at starting dose level, but with improvement compared to preceding findings. Complete missions occurred in 73% (11 of 15). By then, all patients had received dose reductions: in one case treatment continued at 200 mg per day, 4 of 15 patients continued at 150 mg per day and 10 of 15 patients at 100 mg per day. After 24 weeks of therapy polyps have not been documented. After 24 and after 30 weeks, there were 2 of 15 patients with partial remission and 86% (13 of 15) of the patients with complete remission. After 42 weeks of therapy there were 5 of 15 patients with partial remission receiving 100–50 mg per day and 11 of 15 patients with complete remission receiving 50–25 mg per day (Figure 1). An increase of number of patients at a dose of 100 mg per day after 42 weeks of therapy might indicate the lowest effective dose in certain cases.

All patients in the control group (10) underwent 3 examinations at 3 month intervals. At every examination polyps were documented proctoscopically and confirmed by histologic sections in all patients, with a mean of nearly 10 polyps/examination per patient (range 3–13 polyps). These results are to be classified as "no regression". The comparison to the results between groups after 42 weeks of treatment was, therefore, striking.

Side-effects

Treatment with sulindac was well tolerated. None of the patients had to terminate treatment due to toxic side-effects. A mild gastritis occurred in 2 patients treated with sulindac at the highest dose level. This responded to treatment with antacids (calcium carbonate and aluminium-hydroxyd gel) for 4 weeks, and did not relapse during

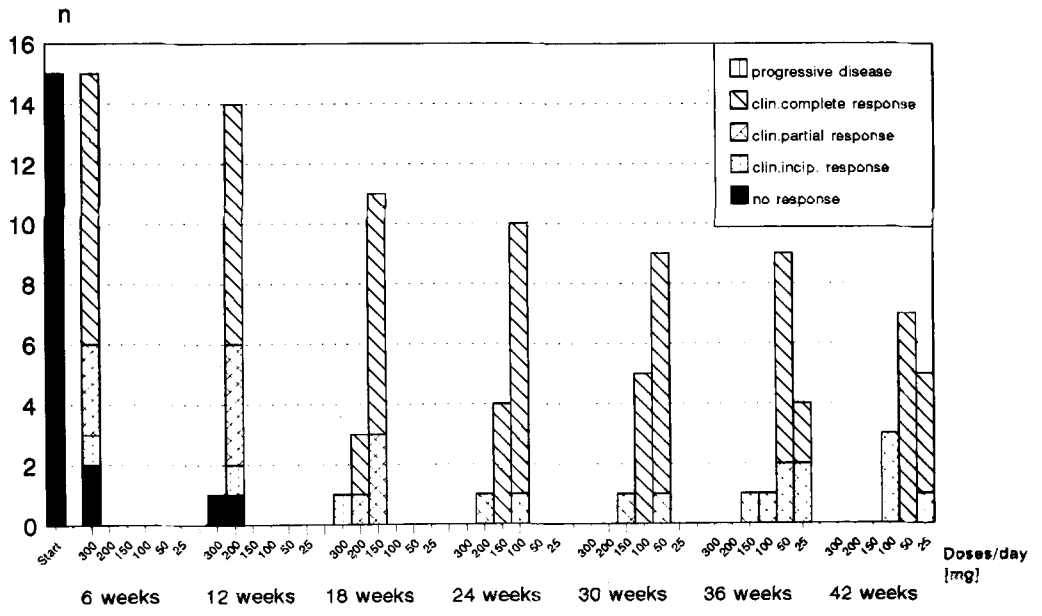

Fig. 1. Proctoscopic findings colectomy with ileorectal anastomosis for FAP during follow-up of 42 weeks ($n = 15$). Starting dose level was 300 mg Sulindac daily. The dose was reduced in predefined steps according to proctoscopic results. The columns show the therapeutic effect of the doses administered at the preceding examination. E = Examination, the number indicates the length of the follow-up period in weeks (e.g. E12 = examination after 12 weeks of therapy)

further treatment at lower dosage of sulindac. No other clinical or laboratory toxicities were observed.

Histologic confirmation of the proctoscopic results, proliferation kinetics, fractionated prostaglandin analysis of the mucosal biopsies and sulindac level analysis in biopsies are nearly concluded and will soon be published.

Discussion

Spontaneous resolution of rectal adenomas after colectomy with IRA has been observed in many cases, leading to a disease – free interval during follow-up in some cases up to several years [14–17]. The reason for spontaneous adenoma reversion is a subject of discussion and hypothesis. The most reasonable theory seems to be the change of fecal flora, bile acid and coprosterol concentration [14], but also changes in dysplasia – promoting factors within the mucosa may be induced by colectomy. However, absence of adenomas in the rectal remnant does not eliminate the risk of rectal cancer. The chance of recurrence of adenomas increases with length of follow-up [5, 14]. The major disadvantage of colectomy with IRA still remains life-long surveillance with at least annual proctoscopy, polypectomy or fulguration [1, 4, 14]. Sulindac, a non-steroidal anti-inflammatory drug (NSAID), a cyclooxygenase inhibitor, significantly decreased the incidence and number of intestinal adenomas induced by dimethylhydrazine in Balb/C mice or in rats [18, 19] possibly acting via inhibition of prostaglandin synthesis, since human tumours of the large bowel contain more prostaglandins than the adjacent mucosa [20].

Several contributions describe oral application of sulindac, reversing adenomas in FAP at doses of 150–400 mg daily, affecting not only rectal adenomas after colectomy and IRA, but even adenomas in non-operated colons. The size and numbers of colonic or rectal adenomas was reduced totally or nearly totally. Gastric or duodenal adenomas, as extracolonic manifestation of FAP, seemed to remain unchanged [7, 9, 13]. In none of the published cases was progressive disease or lack of response to therapy found during sulindac therapy. A placebo-controlled randomized study with oral sulindac for two 4-month periods confirmed these findings [12]. Recurrence of rectal adenomas was described 3–4 months after sulindac therapy, with one case developing recurrence after 19 months of follow-up. Some reports suggest that maintenance therapy is required to perpetuate adenoma regression. Because of possible side-effects of oral NSAIDs, rectal administration was preferred.

To our knowledge, this may be the first study to describe rectal application of sulindac in FAP after colectomy and IRA and has shown prolonged effect after dose reduction. No progressive disease occurred, and all cases responded to therapy after 12 weeks; 3 of 15 cases had clinical partial regression after 6 weeks; 9 of 15 cases had complete clinical remission after just 6 weeks of treatment. By 18 weeks of sulindac therapy doses were reduced in all cases. Up to now no recurrence of visible adenomas occurred on low-dose sulindac therapy. An important further observation was that patients with severe colorectal polyposis and with distinct gastroduodenal polyposis showed a delayed response to sulindac.

An observation period of only 3 months seems inadequate [13], for some patients proved incipient response after 3 months of therapy in worst cases of rectal adenomas, as indicated in our study. Maintenance therapy at doses of 25–50 mg daily seems to be effective at present; in the case of a recurrence the application of 100 mg sulindac daily is planned.

Sulindac, a prodrug to the active metabolite, might have advantages over other NSAIDs, even in colectomized patients, but an intact colon seems to be necessary, both for conversion to the active metabolite and for absorption [21]. This prerequisite of the metabolism of sulindac cannot be confirmed, because the effect observed occurred in operated patients, usually leaving a

remnant of only 12 to 15 cm of intact rectal mucosa for absorption. So the question remains, whether the active metabolite, sulindac-sulfide or the prodrug acts upon adenomas [12]. Neither the exact mechanism of antiproliferative activity of sulindac, nor the effective dose required for response, is established. It still remains unclear whether the same effect could be achieved with rectal low-dose sulindac on a regular regimen or with a high initiation dose of sulindac at entry and early reduction to low-dose therapy. Results of the latter study are being prepared. The long-term effect of low-dose sulindac on proliferative activity of adenomas cannot be anticipated. It may be presumed that a low-dose local NSAID effect on the mucosa with selective prostaglandin inhibition or possibly angiogenesis inhibition [22, 23] may control adenomatous activity. The evaluation of local influence of distinct NSAID-doses on adenomatous proliferation and mucosal prostaglandin expression provides new aspects concering the mechanism of action. Sulindac is more effective than ascorbic acid or 5-Fluorouracil in FAP adenomas [24, 25].

Side-effects of rectal administration of sulindac are rare and were only seen at starting dose levels in 2 cases (gastritis). This unwanted effect may not corroborate completely with the experimental result, that sulindac applied rectally in rats exerted no gastric ulcerogenicity in contrast to indomethacin, diclofenac, ibuprofen and ketoprofen [26]. No side-effect on bone marrow, liver- and renal function was documented as a result of rectal sulindac therapy. No studies with oral sulindac in FAP reported on laboratory tests or side-effects [7, 9, 12]. Side-effects of sulindac in rheumatic disorders with regular doses of 300–400 mg daily are well described [17], but seem to be rare in FAP, despite a long-term therapy; the recent studies were not clear on this point [7, 9].

For the near future adenoma regression after rectal sulindac application may be useful in controlling proliferative (dysplastic or adenomatous) activity of the mucosa after colectomy with IRA. This procedure is uncomplicated, morbidity rates are low, functional outcome is very good, even in the elderly [2, 3, 27, 28]. Soiling, incontinence, night evacuation, incontinence at night and catheter evacuation are still problems after restorative proctocolectomy, resulting in less than optimal function. Morbidity rates from 10–40% have been described; postoperative complications, e.g. pelvic sepsis, anastomotic leakage or narrowing, small bowel obstruction, are more frequent than after colectomy with IRA [4, 29–33]. If adenoma regression could be assured by locoregional sulindac therapy, this regimen should be provided as a consecutive therapy after colectomy with IRA, at least after re-development of adenomas. The latter surgical procedure then could be advised as bearing the lowest risk, or making a salvage proctocolectomy unnecessary, since progressive disease in the rectum could be controlled. Lifelong surveillance of the rectal mucosa after colectomy with IRA is required, but time intervals between proctoscopic re-examinations might increase and the number of polypectomies or fulgurations might decrease. The risk of bleeding and perforation could be decreased [13]. The incidence of rectal cancer after colectomy with IRA varies from 3 to 59%, with more after longer follow-up periods [1–3, 5, 34, 35].

Further studies should establish the most suitable NSAID and its application and efficacy in long-term low-dose usage in the hope of controlling the proliferative activity and dysplasia of adenomatous mucosa and diminishing cancer risk in these patients.

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