NSAIDs and colorectal cancer prevention

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This article discusses the merits and limits of nonsteroidal antiinflammatory drugs (NSAIDs), including cyclooxygenase (COX)-2 inhibitors, for colorectal cancer prevention. The suppressive effect of NSAIDs on colorectal tumors has been recognized since as early as 1981. The chemopreventive effect of NSAIDs on colorectal tumors in relationship to the inhibition of prostaglandin synthesis is reviewed first. Then, the results of a randomized double-blind clinical test that examined the regressive effect of a COX-2-specific inhibitor on adenoma of familial adenomatous polyposis (FAP) are presented. Other similar trials are also reviewed. The clinical guideline for the use of aspirin, NSAIDs, and COX-2 inhibitors for primary prevention of colorectal cancer that was prepared for the U.S Preventive Services Task Force is introduced. These results suggest that a higher dose of COX-2 inhibitors has a suppressive effect on adenoma of the colon and rectum, although a moderate clinical dose of COX-2 inhibitors does not induce clinically effective suppression of adenoma. In the future, NSAIDs may be tried in combination with other materials to prevent colorectal cancer.

Key words: COX-2 inhibitor, colorectal cancer prevention, familial adenomatous polyposis, adenoma

Introduction

Colorectal cancer prevention strategies can be classified into three categories. The first category is the established and practical method of screening high-risk groups for colorectal cancer. The other two methods are chemoprevention based on epidemiological knowledge and cancer prevention based on genetic knowledge. The latter two need to be improved and have not yet been practically applied. In all three methods, colorectal adenoma may be a target of evaluation for prevention of colorectal cancer.

A historical overview of NSAIDs and colorectal cancer prevention

Chemoprevention of colorectal cancer with nonsteroidal antiinflammatory drugs (NSAIDs) was first reported in 1981 by Narisawa, a Japanese surgeon. Narisawa et al. reported that chemical carcinogenesis in rats can be suppressed by indomethacin. Concerning the prevention of adenoma in familial adenomatous polyposis (FAP), Waddell et al. reported in 1989 that almost all polyps were eliminated by sulindac in four of seven FAP patients. Earlier than these reports, John Vane revealed that aspirin-like drugs have an inhibitory mechanism on prostaglandin synthesis, for which work he won a Nobel Prize in 1982. Cyclooxygenase-2 (COX-2) is one of the first-stage prostaglandin synthetases.

Prostaglandin-related factors and colorectal tumors

Before discussing the effect of COX-2 inhibitor on adenoma, it is convenient to review the relationship between prostaglandin-related factors and colorectal tumor (Fig. 1). Recent studies have clarified that colorectal adenoma originated from loss of function of the APC gene. A range of laboratory investigations suggest that COX-2 plays an important role in colorectal carcinogenesis and its metastases. COX-2 increases prostaglandins and the vascular endothelial growth factor,
Colorectal tumor and related factors

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**Fig. 1.** Colorectal tumor and related factors. COX-2, cyclooxygenase 2; PGE₂, prostaglandin E₂; VEGF, vascular epithelial growth factor; APC, gate-keeping gene against adenoma

VEGF⁵ COX-2 knockout suppresses colorectal tumor in APC knockout mice.⁵

It is well known that prostaglandins and prostacyclin are synthesized from arachidonic acid with the help of COX-1 and COX-2. Arachidonic acid is one of the three essential fatty acids. Naming of fatty acids is determined according to the arrangement of their carbon atoms. The first double bond position of a fatty acid is counted from the tail or the omega site of the carbon atom chain. The total number of carbon atoms of the fatty acid comes next, then a colon followed by the total number of double bonds. Consequently, arachidonic acid is an omega-six fatty acid that is composed of 20 carbon atoms and 4 double bonds (Fig. 2).

Prostaglandin E₂ is an important prostanoid descended from arachidonic acid. Prostaglandin E₂ induces (1) gastric mucosal secretion, (2) positive modulation of inflammation, (3) positive control of cell growth, and (4) strong contraction of the smooth muscle. Many of these features may promote the growth of colorectal tumor cells as well as normal gastrointestinal stem cells.

**A trial to see whether a COX-2 inhibitor induces clinically sufficient suppression of adenomas in patients with FAP**

Based on this background information, there was interest in the effects on adenoma in patients with FAP when a COX-2 inhibitor is administered. Therefore, a study to elucidate these effects was planned.

The aim was to determine whether a moderate dose of a selective COX-2 inhibitor is clinically effective in suppressing adenoma in patients with FAP. There are several conditions that are required to obtain an accurate and stable measurement in this kind of trial. First, the test must be conducted under double-blind placebo-controlled circumstances. Second, preparation of the colon should not induce edema in the colonic mucosa. Third, the target area should be clearly identifiable. Fourth, a dye-spraying method should be used. Fifth, last but not least, direct measurement should be applied.

It is not easy to evaluate the change in the size or the number of polyps at a specific site of the large bowel over several months. Polyp size should not be compared between two simple photographs because there are several factors that affect polyp size measurements, namely (1) the distance from the endoscope, (2) the viewing direction or angle, and (3) the amount of air inflation. For example, the two pictures in Fig. 3 show the same site. The picture on the right side was taken 6 months after one on the left. Some polyps seem to have changed in size as much as 50% from the polyps before the treatment. Direct measurement revealed that actually the size of these polyps had not changed.

The study was a multi-institute, randomized, double-blind, placebo-controlled trial.⁷ Sixty-one patients with FAP were assigned to three groups and given medication over 26 weeks. One medicated group was given 150 mg COX-2 inhibitor tilacoxib once daily and the other medicated group was given 200 mg tilacoxib once daily. The placebo group was given capsules that were identical in appearance with those given to the medicated groups. Those doses are regular clinical doses for rheumatoid arthritis. Percent change in polyp number and polyp size were the primary endpoints of our study. Adverse events were evaluated as a secondary endpoint.

The study was conducted according to the CONSORT method.⁸ Twenty one, 19, and 21 cases, respectively, were randomly allocated to each group; 90% to 95% of these patients met the selection criteria for the analysis of the effects of medication (19, 20, and 18 cases). The number of polyps in the placebo group changed from a baseline of 0% to 67%, and the median was 0%. The two treatment groups showed no significant difference from the placebo group in changes in polyp number. The change in polyp size in the placebo group ranged from −33% to 40%, and the median was 0%. The two trial groups showed no difference from the placebo group in changes in polyp size (Table 1).

Table 2 shows the comparatively frequent complaints that were recorded, with abnormal data considered to be specific adverse events to COX-2 inhibitors. Among them, cold symptoms, diarrhea, stomachaches, and decreased hemoglobin were more common in the test groups compared with the placebo subjects. These events were mild, and discontinuation of treatment during the test period was judged to be unnecessary.