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Piroxicam and Other Cyclooxygenase Inhibitors: Potential for Cancer Chemoprevention

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Abstract Piroxicam is a nonsteroidal anti-inflammatory drug (NSAID) widely used for treatment of inflammatory arthritis. Recent experimental and clinical studies suggest that piroxicam, as well as other NSAIDs, may be useful for chemoprevention of colon cancer. While there is less information regarding NSAIDs for chemoprevention of urinary bladder malignancy, there are compelling data which suggest that this should be evaluated.

A major effect of NSAIDs is inhibition of cyclooxygenase, the rate-limiting enzyme for conversion of arachidonic acid to important signal molecules, including prostaglandins, which profoundly affect cellular functions in many tissues. The initial enzyme reaction leading to formation of prostaglandin H can be accompanied by cooxidation of xenobiotics resulting in extrahepatic and local tissue production of reactive products which are carcinogenic. The end product prostaglandins, especially prostaglandin E_2 (PGE_2), are biological modifiers which can significantly affect cell proliferation and tumor growth. High levels of PGE_2 stimulate growth of certain tumor cell lines while inhibition of prostaglandin synthesis with indomethacin or piroxicam can cause suppression. The mechanisms for this effect are unclear. Studies in cultured cells exposed to indomethacin show inhibition of G_1-to-S phase progression of the cell cycle and a reduction in overall DNA synthesis. It is unclear whether this effect on cell growth results from some direct action of the NSAID or a reduction in prostaglandins or indirectly from modulation of important control signals, such as calcium flux. In addition to cyclooxygenase, NSAIDs can inhibit activity of other enzymes, including phosphodiesterases and cyclic GMP-AMP protein kinases, which may be central to cancer initiation and promotion. NSAIDs can also interfere with transmembrane ion fluxes and with cell-to-cell binding.

Prostaglandins can modulate a variety of immunological responses and thereby play an important role in host antitumor immunity. For example, high levels of tissue PGE_2 are frequently associated with suppression of immune surveillance and killing of malignant cells. Conversely, immune responses are generally enhanced by drugs that inhibit prostaglandin synthesis. PGE_2 can act as a feedback inhibitor for cellular immune processes, such as T-cell proliferation, lymphokine production, and cytotoxicity. This effect is also seen for macrophage activity and natural killer cell toxicity. In general, either increased production of PGE_2 or increased sensitivity to normal amounts of PGE_2 results in depressed cellular immunity. Cyclooxygenase inhibitors (NSAIDs) such as piroxicam which decrease PGE_2 production can stimulate cellular immune function both *in vitro* and *in vivo*.

A variety of tumor cell lines and human malignancies produce large quantities of prostaglandins. Of interest, the concentration of PGE_2 is increased in certain premalignant lesions, such as benign adenomatous colon polyps, and further increased in cancerous colon tissue. This observation, taken in context with the effects of prostaglandins on tumor cell growth and immune surveillance, provides strong rationale for study of NSAIDs as potential agents for colon and bladder cancer chemoprevention.

During the last decade, more than a dozen animal studies have shown significant protection against development of colon cancer by treatment with NSAIDs piroxicam, indomethacin, and sulindac. Other studies have shown that aspirin protects rats given known carcinogens against colon and bladder cancer. Moreover, patients with familial adenomatous polyposis who are at high risk for colon cancer have, in many instances, experienced regression of colon adenomas during treatment with NSAIDs, particularly sulindac. Most recently, two large epidemiological surveys have reported compelling evidence which suggests the NSAID aspirin may have significant protective activity against colon cancer.

This presentation will summarize the rationale for use of piroxicam and other inhibitors of cyclooxygenase as cancer

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chemoprevention agents and will briefly review results of our approach to evaluating piroxicam as an agent to prevent colon cancer. With this as background, the potential for NSAIDs in chemoprevention against bladder cancer will be explored.

Key words: adenomatous polyps, carcinogen activation, colon cancer, indomethacin, nonsteroidal anti-inflammatory drugs, prostaglandin H synthase, sulindac, urinary bladder cancer, xenobiotics

Considerable evidence suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) which inhibit cyclooxygenase may have an important role in chemoprevention of both bladder and colon cancer. This possibility has a strong conceptual basis and is supported by results of experimental studies in animal models of carcinogenesis and in drug treatment and epidemiological studies in humans. This review initially considers the rationale for using NSAIDs in cancer chemoprevention and then briefly discusses our developmental studies using piroxicam as a chemoprevention agent for colon cancer. The approach appears to have relevance for chemoprevention of bladder cancer.

ACTIVATION OF CARCINOGENS BY CYCLOOXYGENASE

The best-characterized pharmacological effect of NSAIDs is inhibition of the enzyme prostaglandin H synthase (PHS) or cyclooxygenase, which catalyzes the first step in conversion of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. While changes in tissue levels of these important biological modifiers were initially considered the primary effect of cyclooxygenase inhibition which in turn conferred protection against cancer, attention has recently been focused on the initial steps of the cyclooxygenase reaction itself [1].

PHS has two distinct enzymatic activities: fatty acid cyclooxygenase and prostaglandin hydroperoxidase [2]. In the presence of oxygen, the fatty acid cyclooxygenase component of the enzyme initially catalyzes the bisdioxygenation of arachidonic acid to the cyclic endoperoxide prostaglandin G_2 (PGG_2), the first product in the arachidonic acid metabolic cascade. The peroxidase activity then reduces the hydroperoxide to the alcohol, PGH_2, which is subsequently converted to other prostanoids, including PGE_2, prostaglandin $F_{2\alpha}$, prostacyclin and thromboxanes [1]. During the early peroxidase reaction, free radicals are produced which may damage cells. Also, if present, xenobiotic cosubstrates, such as aromatic and heterocyclic amines, are co-metabolized to reactive products which may be carcinogenic [1,3,4].

PHS has been localized subcellularly to the endoplasmic reticulum and nuclear membranes [5], a position that makes sensitive nucleic acids readily accessible to attack by the reactive products produced by cooxidative metabolism. Thus, PHS may play a role in carcinogenesis by activating procarcinogens to electrophiles that bind DNA. In relation to colon cancer, PHS activates IQ, a specific heterocyclic aromatic amine found in food, to reaction products that are mutagenic. Treatment with the NSAID indomethacin blocks activation of IQ and confers protection against colon cancer induced by this substance [3]. Similar observations have been reported for another NSAID, aspirin, in studies with the colon carcinogen 1,2-dimethyl hydrazine (1,2-DMH) [6,7] and with the bladder carcinogen *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]-formamide (FANFT) [8,9]. Inhibition of PHS-linked carcinogen activation by NSAIDs appears to be a potentially important mechanism for protection against cancer, especially in the colon and urinary bladder.

NSAID EFFECTS ON CANCER CELL GROWTH

That NSAIDs may also protect against cancer by affecting steps distal to carcinogen activation and tumor initiation is suggested by results of studies with indomethacin and piroxicam. These drugs demonstrate protection against colon cancer, even given days to months after carcinogen treatment when microscopic lesions are already present in colon mucosa [10–12]. These findings strongly suggest that NSAIDs exert a protective mechanism in the promotion phase of tumorigenesis. NSAIDs have been noted to affect cell proliferation in a variety of experimental models that may give some insight into

the process. For example, several NSAIDs have been shown to directly inhibit growth of rat hepatoma and human fibroblast cells in culture [13], and to suppress transplantable murine colon adenocarcinoma [14]. In these studies, cell viability was not impaired and growth inhibition was reversible. Later, indomethacin was also shown to arrest the G_1–S phase progression in the cell cycle of cultured cells and to reduce overall DNA synthesis [15,16]. NSAIDs may also affect carcinogenesis by modifying the activity of enzymes other than cyclooxygenase. For example, they inhibit phosphodiesterase and cyclic AMP protein kinase, both of which may be integral to cancer initiation and promotion [17,18].

NSAID EFFECTS ON IMMUNE FUNCTION

Influencing immune function is another potentially important effect. Treatment with NSAIDs has been shown to enhance a variety of immunological responses which may restore antitumor immunity in the compromised host. Most of these effects are thought to occur secondary to a reduction in tissue prostaglandins [19]. Prostaglandins can modulate immune system function through a variety of mechanisms [20]. Of all arachidonic acid metabolites, only PGE_2 appears to have a defined role in the regulation of cellular and humoral immune responses [20,21]. Immune surveillance and killing of malignant cells can be suppressed by high tissue levels of PGE_2, whereas immune responses are generally enhanced by drugs that inhibit PGE_2 synthesis [20–23]. PGE_2 also can act as a feedback inhibitor for cellular immune processes, such as T-cell proliferation, lymphokine production, and cytotoxicity [24]. This effect of PGE_2 is also true for macrophages and for natural killer cell cytotoxicity [25]. In general, either increased production of PGE_2 by tumors or increased sensitivity to normal amounts of PGE_2 appear to be associated with depressed cellular immunity [21]. Conversely, NSAIDs which inhibit cyclooxygenase and decrease PGE_2 production often act as a stimulus for cellular immune function, both *in vivo* and *in vitro* [20,26]. Thus, NSAIDs have been shown to diminish growth of malignant cells by a direct effect on the cell and to enhance immune surveillance in the cancerous tissue [20,26]. All of these mechanisms appear important and potentially complementary for cancer prevention.

CONCENTRATION OF CYCLOOXYGENASE IN NORMAL AND NEOPLASTIC TISSUE

Cyclooxygenase is present in cell membranes of most body tissues. Perturbation of membrane structures stimulates phospholipase activity and release of free arachidonic acid from phospholipid stores. The activity of cyclooxygenase in tissue is roughly reflected by the concentration of its metabolic end products. Significant cyclooxygenase activity has been reported in both the urinary bladder and in colon mucosa as reflected by prostaglandin concentration in these tissues [27,28]. Of note, synthesis of prostaglandins is increased during malignant transformation and tumor cell growth [29]. In bladder mucosa, prostaglandin synthesis occurs in transitional epithelial cells [8], while in the colon, prostaglandins are produced mainly by connective tissue cells in the mucosal stroma and not the epithelium [30]. However, in colon neoplasms the exact cell type responsible for prostaglandin synthesis is unclear. We recently noted the presence of a hierarchical relationship between the concentration of prostaglandins in tissue biopsies and the progression from normal mucosa to adenomatous polyps to cancer [31]. Mucosal biopsy specimens obtained during fiberoptic colonoscopy were snap-frozen in liquid nitrogen and assayed for PGE_2 with a commercial radioimmunoassay kit (Advanced Magnetics, Boston, MA). PGE_2 concentration in the normal-appearing colorectal mucosa was similar in patients with adenomatous polyps (164.7 ± 24 pg/mg tissue) and with colon cancer (147.2 ± 39.5 pg/mg tissue). PGE_2 concentration was significantly increased in adenomatous polyp tissue (227.3 ± 41.3 pg/mg tissue; $p = 0.018$) and was even greater in colon cancer tissue (440.1 ± 68.9 pg/mg tissue; $p = <0.0001$). This observation in normal, adenomatous, and malignant colon tissues shows that large amounts of PGE_2 are produced by colon neoplasms and may affect progression to cancer by stimulating cell growth and impairing immune surveillance. It is possible that this same relationship is present in bladder neoplasms.

The observation that adenomatous colorectal polyps demonstrate a PGE_2 concentration inter-

mediate between malignant tissue and normal mucosa is of particular interest, since colorectal carcinogenesis appears to involve a multistep process in which the adenoma is a transitional lesion [32]. It is conceivable that, in addition to an increase in the number of PGE-producing stromal cells, epithelial cell genes which control or influence the activity of cyclooxygenase may undergo mutation during malignant transformation and that increased prostaglandin production by malignant epithelial cells contributes to cancer growth.

ANIMAL STUDIES OF CANCER INHIBITION WITH NSAIDs

A variety of studies have evaluated the mechanism by which aspirin inhibits urinary bladder cancer induced by the carcinogen FANFT, with and without sodium saccharine as a promoter. Saccharine significantly increases the number of bladder tumors induced by FANFT [33]. Aspirin, which effectively blocks cyclooxygenase activity, has been shown to decrease the activation of FANFT to a more proximate carcinogen. A protective effect is seen mainly when the cyclooxygenase inhibitor (aspirin) is administered prior to or concomitant with FANFT.

Studies with colon carcinogens also show significant inhibition of cancer formation by NSAID treatment, but the mechanism of action is less clear. Since 1980, numerous investigators have reported that treatment with indomethacin, piroxicam and sulindac (all drugs which reduce prostaglandin synthesis by inhibiting activity of cyclooxygenase) effectively reduced tumor incidence and growth of colon polyps and cancer in the rat induced by a variety of carcinogens [10–12,34–39]. Similar results were obtained with aspirin inhibition of FANFT-induced bladder cancer; when the NSAID was given at the same time as the carcinogen, tumors were effectively suppressed. However, in a number of the studies mentioned above, the NSAID was first administered days to weeks after the carcinogen and a protective effect was still evident. Of particular note is the study by Reddy [12] which not only demonstrated a strong dose-response relationship between the amount of the NSAID piroxicam given with food and the development of colon cancer following treatment with 1,2-DMH, but also showed a significant decrease in the incidence of neoplasms by piroxicam even when drug treatment was not initiated until 13 weeks after carcinogen administration. This observation strongly suggests that piroxicam can induce regression of evolving neoplastic foci already present in the colon at the time drug treatment is initiated. Thus the beneficial effects of NSAIDs in preventing tumor formation and growth in colon cancer might result from prevention of carcinogen activation, from direct inhibition of tumor cell growth, or from enhanced immune system killing of abnormal cells. All three potential effects result from a direct action of the NSAID itself or a consequence of diminished levels of prostaglandin in colon mucosa caused by NSAID effects on cyclooxygenase. Which predominates is not clear. Of note, a specific direct effect of NSAIDs on inhibiting malignant cell growth is supported by the results of studies by Narisawa [40] who found that PGE_2 administration neither enhanced nor diminished formation of tumors in the 1,2-DMH model of rodent colon cancer and that supplementation of PGE_2 did not diminish the strong anticarcinogenic effect of indomethacin. If a direct effect of NSAIDs on cancer cell biology is the basis for their inhibition of cancer progression, one could then view suppressed level of prostaglandins in tissue caused by NSAID treatment as a convenient way to estimate NSAID activity in the specific tissue of interest. This could also be a convenient way to monitor for drug effect in clinical studies.

HUMAN STUDIES

During therapy of patients with desmoid tumors, some of whom had Gardner's syndrome with colon adenomas and an increased risk of cancer, Waddell and colleagues [41] initially observed that sulindac treatment dramatically reduced the number of colon polyps. Subsequently, Waddell *et al.* [42] reported more extensive experience in treating colon polyps with sulindac in patients with Gardner's syndrome and familial adenomatous polyposis (FAP). The authors observed either an impressive reduction or complete resolution of colon adenomas during drug treatment. In addition, none of the patients developed colorectal cancer during the treatment period, which in a few cases exceeded

six years. Of interest, three patients developed recurrence of colon adenomas when sulindac was discontinued. Reinstitution of drug treatment subsequently led to disappearance of the recurrent polyps. Since this initial report, other investigators have published uncontrolled experiments with sulindac in small numbers of patients with FAP, noting either a significant reduction in the number of polyps or a complete disappearance of the adenomas during sulindac treatment [43–45]. In the recent study by Labayle [44], nine patients with FAP were randomized to sulindac (300 mg/day) or a placebo during two four-month treatment periods. All had undergone prior colectomy with ileorectal anastomosis and had developed recurrent polyps in the remaining rectum. During initial sulindac treatment, there was almost complete regression of polyps in all patients. During subsequent placebo therapy, five of the nine patients demonstrated a recurrence or increase in the number of colon polyps. The reversible clinical response observed in this trial is of interest since studies with cultured cells, and animal experiments of cancer growth, have both shown a return of cell growth patterns present prior to cyclooxygenase therapy after the inhibitor is withdrawn [15,16,46].

Most recently, at least two studies reporting multi-institutional case-controlled drug surveillance studies have suggested that regular NSAID use (mostly aspirin; dosages not defined) significantly reduced the risk of having fatal colon cancer [47,48]. While these reports are intriguing, the NSAID treatment's mechanism of effect is unclear, especially since a beneficial response was observed with as little as three months of NSAID use during the previous year. It is difficult to reconcile this effect with current concepts of colon carcinogenesis which involve transformation from normal colonic mucosa to adenomatous tissue and finally to cancer, a process which is thought to occur over approximately a 10-year period of time [49]. Nevertheless, the compelling data presented by these reports add strong support to a role for NSAIDs in protection against cancer.

SIDE EFFECTS OF NSAID THERAPY

While drugs which inhibit cyclooxygenase and prostaglandin synthesis have had increasing and widespread clinical use for treatment of arthritis during the past 15–20 years, their beneficial effects have been accompanied by a significant occurrence of erosive mucosal disease in the upper gastrointestinal tract [50,51]. In gastric mucosa, prostaglandins promote important defense mechanisms that protect against acid-peptic injury [52]. Treatment with drugs that inhibit cyclooxygenase frequently causes gastric mucosal erosions and occasionally produces significant ulceration, leading to complications such as bleeding and perforation [53]. Accordingly, it seems unlikely that the doses of NSAIDs which are used for treatment of arthritis will be acceptable for long-term cancer chemoprevention in otherwise healthy patients. However, because of the strong rationale for their use as chemopreventive agents, the positive results in animal studies showing protection against induced colon cancer, and the reports of favorable treatment responses in patients with genetic polyposis syndromes at high risk for cancer, we felt it important to pursue further clinical studies specifically evaluating the possibility that low doses of NSAIDs may effectively reduce cyclooxygenase activity in colon mucosa. Piroxicam (Feldene™) was selected for study because of its long half-life which allows once daily dosing, and because of the extensive worldwide clinical experience documenting its safety.

PHASE IIa STUDY OF PIROXICAM

Volunteers (ages 40–80) who had one or more adenomatous colon polyps removed within the preceding 10 years and who were otherwise healthy were recruited to participate in a single-blind, continuous-treatment study. The protocol was approved by the University of Arizona Human Subjects Committee, the U.S. Food and Drug Administration, and was sponsored by the National Cancer Institute (NCI-P01-CA41108). Piroxicam and matching placebo were provided by Pfizer, Inc. All patients were treated with placebo for one month and then piroxicam at one of four doses (5, 7.5, 10, or 20 mg/day) for three additional months. Biopsies of the upper rectal mucosa (15–18 cm from anal verge) were obtained through a fiberoptic sigmoidoscope from normal-appearing rectal tissue using standard biopsy forceps. Specimens were

obtained at the beginning and end of the placebo run-in, and again after 1 and 3 months of piroxicam treatment.

Mucosal biopsy samples for PGE_2 analysis were snap-frozen in liquid nitrogen as soon as they were obtained. PGE_2 was measured by radioimmunoassay (RIA) using a commercial kit, as noted previously. For this, mucosal specimens were homogenized in Tris-ethylene-diamine-tetraacetic acid buffer, methanol was added and the mixture was acidified with formic acid. PGE_2 was then extracted with chloroform and quantitated in duplicate by the RIA using phosphate buffer and dextran-coated charcoal for separation of free and bound prostaglandin.

To assess patient adherence to drug treatment and for correlation with observed suppression of rectal mucosal PGE_2, the blood concentration of piroxicam was measured by high pressure liquid chromatography. Serum samples were obtained at the time of the rectal mucosal biopsies, extracted with methanol, dried under nitrogen, and reconstituted with the mobile phase (40% acetonitrile, 5% acetic acid, and 55% water). The sample was injected into a high pressure liquid chromatograph equipped with a Waters μBonda Pak C18 column (Altex; Beckman Instruments, Inc.). Isoxicam was used as the internal standard. Drug level was quantitated using a Hitachi spectrophotometer at 352 nm. Dietary assessment by the Arizona Food Frequency questionnaire and 7-day diet recalls also provided evidence for dietary and medication adherence.

The effects of treatment with piroxicam (20 mg/day) for 4 and 12 weeks on the concentration of PGE_2 in rectal mucosa are shown in Figure 1. Four weeks of piroxicam treatment suppressed PGE_2 concentration to approximately 50% of the control or baseline value ($p < 0.05$). Continued drug treatment for eight more weeks caused only slight additional suppression. The initial studies utilized the two commercially available dosage forms of piroxicam, 20 mg/day and 10 mg/day. An additional dosage level of 5 mg/day was prepared by the research pharma-

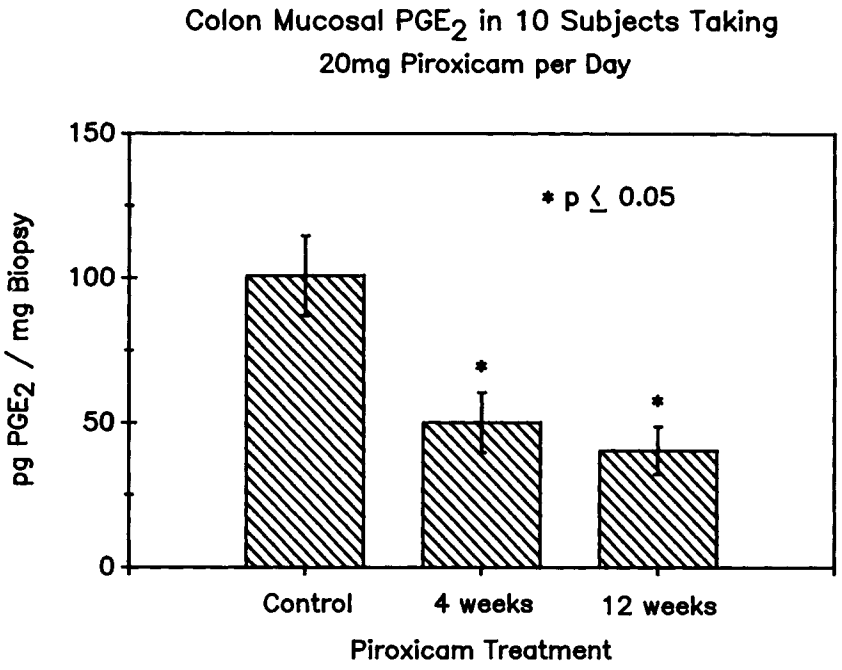

Fig. 1. Effects of treatment with 20 mg/day of piroxicam on PGE_2 concentration in rectal mucosal biopsy specimens obtained during fiberoptic sigmoidoscopy from ten patients with adenomatous colon polyps. Biopsies were taken at the beginning and end of a 1-month control period and again after 4 and 12 weeks of piroxicam treatment. The rectal mucosa was cleansed with a 150 mg saline enema prior to biopsy. Mucosal samples were snap-frozen in liquid nitrogen as soon as obtained and PGE_2 analyzed by radioimmunoassay.

cy. Figure 2 shows the observed dose-response relationship in rectal mucosal PGE_2 concentration induced by the three piroxicam doses. The 5 mg dose gave inconsistent results which were not statistically different from control. The effect of the 10 mg dose, however, exceeded the targeted goal of 20% reduction in PGE_2. Accord-20% reduction in PGE_2. Accordingly, a 7.5 mg dose was prepared and tested in an additional 11 subjects. Figure 3 shows that ingestion of 7.5 mg of piroxicam daily induced a progressive and satisfactory reduction in colon mucosal PGE_2 concentration. There was no evidence for tachyphylaxis or a reduction in the inhibiting effect of the 7.5 mg/day dose of piroxicam on rectal mucosal PGE_2 concentration over the relatively short duration of this study.

During treatment with piroxicam at 20 mg/day, blood piroxicam levels averaged 10–12 μg/mL. This blood level was considerably greater than blood piroxicam concentrations achieved during the 7.5 mg dose, which usually fell between 2 and 4 μg/mL. Nevertheless, the lower oral dosage of piroxicam and resultant lower blood concentration of the drug was sufficient to induce a significant biological effect on colon mucosa as reflected by the reduction in PGE_2 concentration.

Evaluation of safety parameters throughout the 4-month study showed no significant drug-related side effects, no clinical evidence (symptoms) of erosive gastric mucosal disease, no development of significant adverse symptoms, and no evidence of any induced biochemical abnormality. As a result, the 7.5 mg/day dose of piroxicam was chosen for continued study in a phase IIb trial (randomized, intermediate marker study), which involves 100 patients treated for a period of three years. The goals are to quantify the effects of drug treatment on mucosal PGE_2 concentration and on epithelial cell proliferation as measured by bromodeoxyuridine staining, as well as to gain more experience with clinical side effects of chronic NSAID treatment in persons without chronic arthritis and pain. Patients are also monitored by colonoscopy after one and three years for evidence of polyp recurrence.

These studies with piroxicam in patients with resected adenomatous colon polyps could also

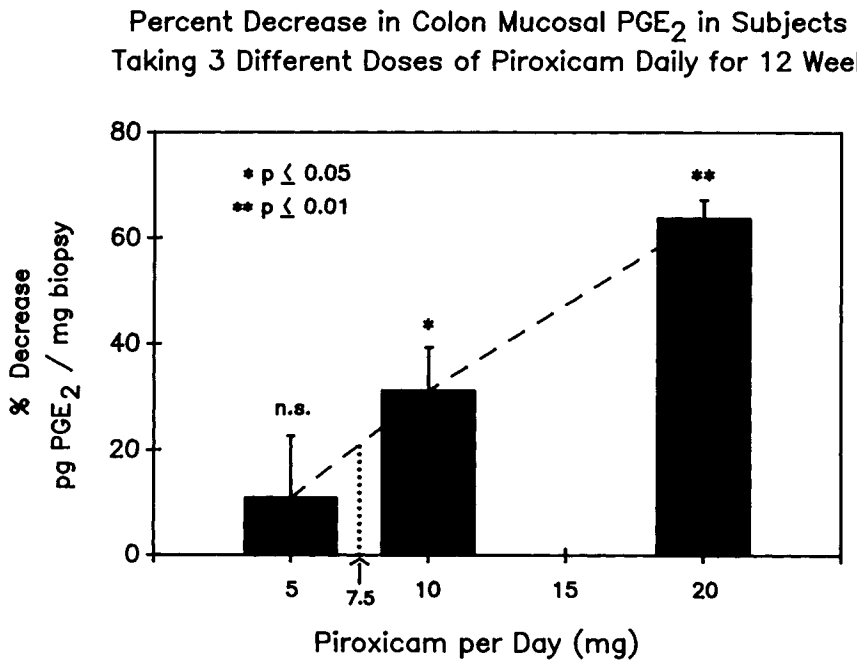

Fig. 2. Percent decrease in rectal mucosal PGE_2 concentration in subjects taking 3 different doses (n = 10/dose) of piroxicam daily for 12 weeks. Biopsies of the mucosal specimens were handled as described in Figure 1.

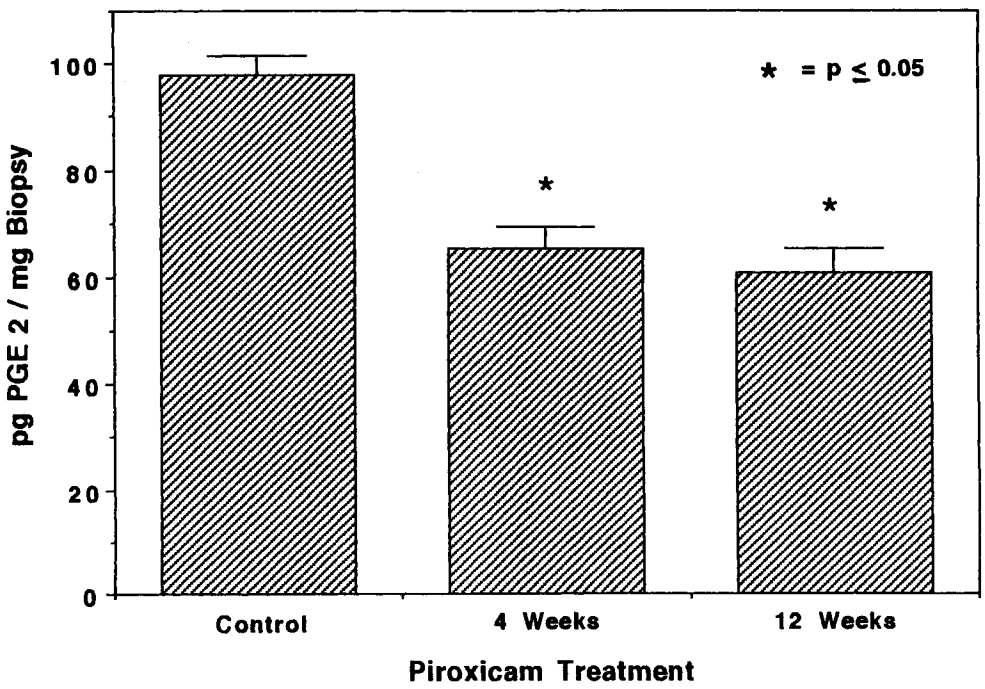

Fig. 3. Rectal mucosal PGE_2 concentration in 11 subjects treated with 7.5 mg piroxicam daily for 0, 4, and 12 weeks. Procedure for mucosal biopsy and PGE_2 analysis was as noted in Figure 1.

serve as a model for future studies with NSAIDs in patients with benign urinary bladder tumors or those otherwise believed to be at increased risk for development of bladder cancer. The high incidence of upper gastrointestinal toxicity that occurs with standard doses of current NSAIDs provides strong rationale for an initial dose-reduction study to find the lowest drug dose which effectively modifies risk factors in bladder mucosa. Such studies are conceptually feasible in view of the ability to obtain specimens of bladder mucosa by cystoscopic biopsy.

DISCUSSION

Multiple lines of evidence suggest that drugs (NSAIDs) which inhibit cyclooxygenase activity and reduce tissue concentrations of prostaglandins, especially PGE_2, have significant potential for beneficially modifying cellular responses to carcinogens and for improving tissue resistance to neoplastic transformation and its progression to cancer. Many different types of malignant cells synthesize large amounts of prostaglandins, especially PGE_2, which can act as a growth promoter for the tumor cells as well as associated vascular and stromal elements [54]. High levels of PGE_2 in tissue also exert a suppressive effect on important immune responses that might effectively kill malignant cells [20,21,26, 32]. Suppression of cyclooxygenase activity by NSAID therapy could reduce carcinogen metabolism and direct effects in tissue as well as impair growth of malignant cells and, by reducing PGE_2 concentration, enhance immune surveillance. The impressive results of NSAID treatment in animal models of carcinogen-induced colon and bladder cancer provide strong support for clinical application of this chemoprevention approach. To date, trials of NSAID chemotherapy in humans have been limited to patients with familial forms of colon cancer; namely, Gardner's syndrome and FAP. Results of NSAID therapy in these patients are impressive and provide a compelling rationale for pursuing additional clinical trials with drugs like piroxicam, sulindac, and indomethacin in other patients at increased risk for developing the more common form of sporadic colon cancer.

Enthusiasm for initiating clinical cancer chemoprevention trials with NSAIDs prescribed at dosages currently used to treat inflammatory arthritis should be tempered by the recognized high incidence of significant upper gastrointestinal tract mucosal damage which can accompany such therapy. The results of our phase IIa dose-finding trial with piroxicam show that a significant biological effect on colorectal mucosa can be achieved with only 7.5 mg daily, a dose which is only one-third the standard arthritis-treatment dose. Since adverse upper gastrointestinal side effects from NSAID treatment appear to be dose-related, this observation is encouraging. However, further results from our current phase IIb trial will be needed to assess whether low-dose piroxicam has a sustained effect and acceptable safety, prior to initiating a large-scale evaluation of it as chemotherapy to prevent recurrence of adenomatous colon polyps and reduce the risk of colon cancer. There is excellent rationale for a similar approach to chemoprevention of urinary bladder cancer with NSAIDs in view of the encouraging results of early prevention studies with aspirin in animal models of cancer.

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