A Nonsteroidal Anti-inflammatory Drug's Effect on the Development of Adenomatous Disease and Cancer of the Colon and Rectum

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A. Aim

The purpose of this study is to assess the effect of sulindac on the development of neoplasms of the colon and rectum.

B. Background

In the United States more than 150,000 people will be diagnosed with colorectal cancer during 1997. Unfortunately, almost of half of these people will succumb to this disease, making colorectal malignancies the second most common cause of cancer death.[1] Except for prophylactic colectomy in certain populations, no proven therapeutic or preventive intervention exists to decrease this high mortality. However, recent epiderniologic, clinical and molecular studies suggest that non-steroidal anti-inflammatory drugs could play a central role in decreasing colorectal cancer death rates.

The understanding of colorectal cancer and its development has been radically altered and clarified over the last twenty years. During this time molecular oncologists have uncovered the basic pathology of neoplasia - the sequential accumulation of mutations in key regulatory genes.[2] Hence, much effort has been put forth to identify the specific genetic alterations which underlie various malignancies. The existence of dominantly inherited forms of colorectal cancer has greatly facilitated the identification of some of the genes specifically involved in colorectal cancer and allowed the generation of mouse models. From this work an overall model of colorectal cancer has emerged in which the pathologic progression from normal epithelium to dysplasia to adenoma to frank carcinoma requires at least seven genetic alterations. [3]

In the epiderniologic arena, workers had long identified dietary and supplemental factors which are associated with lower incidences of gastrointestinal cancers, e.g. high fiber, low fat, certain vitamins and antioxidants. Among the most striking findings are three case control studies which compared the use of non-steroidal anti-inflammatory drugs (NSAID's) between people who developed colon cancer and those who did not. In all three studies, NSAID use was associated with a 40-50% reduction in colorectal cancer and/or mortality.[4,5,6] In one small prospective randomized, double-blind, placebo-controlled study of patients with familial adenomatous polyposis there was a statistically significant 56% decrease in number and a 35% reduction in size of adenomas, following a nine month trial of an NSAID, sulindac 150 mg twice daily.[7]

Recent molecular experiments have provided similar results in murine models of APC and carcinogen induced adenomas and cancer. [8,9,10] While the mechanism underlying these effects has not been delineated, when those same APC mice are genetically altered to lack a functional cylcooxygenase 2 (a target of NSAID's) they have a decrease in adenomas similar to that of NSAID treated APC mice.[8] These data suggest that cyclooxygenase 2 and the products it generates, metabolites of arachiclonic acid play a key role in the progression and development of colorectal adenomas and carcinomas, and therefore, NSAID's may provide a powerful preventive therapy.

C. Hypothesis

Long term, daily use of sulindac will decrease by 40% the development of neoplasms of the colon and rectum among a middle-aged population.

D. Study Design

A prospective, double-blinded, placebo controlled, multi-center study comparing sulindac to placebo with primary end points being the development of colorectal cancer or adenomas, or the need for partial colectomy.

E. Methods

Patient Selection - We will study 12,000 men and women who when they enter the study will be between the ages of 50 - 59. The study will include an equal number of men and woman and will be drawn from the general medicine practice at 10 academic medical centers throughout the country. Each center will need to recruit approximately 60 men and 60 women each of the first five years of the study. Exclusion criteria will include a previous diagnosis of colorectal cancer, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, Peutz-Jeghers syndrome, inflammatory bowel disease, chronic renal insufficiency, cirrhosis, NSAID gastropathy, iron deficiency anemia, allergy to sulindac or NSAID induced bronchospasm. People who chronically take any non-aspirin NSAID's will be excluded from the study, as will anyone who has undergone either a partial or total colectomy. Finally, patients will be excluded if either their primary physician or the study gastroenterologist deem a colonoscopy or light sedation contraindicated.

Patients who have a history of treated *H. pylori* induced ulcer disease will not be excluded, if they have been symptom free greater than six months after completing curative therapy. Although no special effort will be made to recruit patients who have previously had polypectomies, such patients will not be excluded if the pathology is known to show only benign adenomatous changes.

F. Study Protocol

The overall study design will include a screening phase, a short run in period, a treatment period and an observational period. During the screening phase all candidate patients will complete screening questionnaires. In addition to delineating a general medical history and identify patients who meet any of the exclusion criteria, the questionnaire will ask detailed questions about diet, nutrient supplementation, medication history, smoking habits, toxic exposures and family history. At this time all candidate patients will also undergo colonoscopy, have their hemoglobin, serum creatinine, urea nitrogen, albumin, total bilirubin, electrolytes and partial thrombin time measured, and have their stools sampled for occult blood. All polyps will be biopsied. Any patient who has evidence of hereditary polyposis, inflammatory bowel disease, carcinoma, renal insufficiency, cirrhosis or anemia will be excluded from the study.

All eligible patients will begin a run-in period and be given three months of sulindac 150 mg twice daily. They will have their hemoglobin, serum creatinine, urea nitrogen and electrolytes measured at the end of the first and third, eighth and twelfth weeks of the run in period. Their stools will be tested for occult blood during the twelfth week. Any patient 'WITo has evidence of NSAID gastropathy or gastrointestinal bleeding, or who develop azotemia will be not complete the run in period.

Patients who successfully complete the run in period will then be randomized to receive either sulindac 150 mg orally twice daily, or a placebo twice daily. They will continue on this therapy for ten years, and be observed for an additional five years following cessation of therapy.

Every six months the patients will undergo screening for gastrointestinal bleeding with hemocult analysis and blood hemoglobin/hematocrits. Each year the patients will have a physical examination and will complete a study questionnaire similar to the screening questionnaire. At the end of years three, nine and twelve the patients will undergo sigmoidoscopy, and at the end of the sixth, ninth and fifteenth years they will undergo colonoscopy. Patients will be withdrawn from the study if they develop renal insufficiency, NSAID gastropathy, inflammatory bowel disease or colorectal cancer, or if they require colectomy. Patient who develop polyps during the course of the study will them removed and have

therapy as recommended by the American Cancer Society and the American College of Gastroenterology guidelines.

G. Study Medications

Sulindac is a potent reversible inhibitory of cyclooxygenase enzymes, approved by the FDA for use as an antiinflammatory drug. Its most notable side effects are gastropathy and acute renal failure. The relative risk for developing gastropathy among people taking sulindac has be estimated to be three or four times that of the general population[11] However, gastropathy associated with NSAID use usually occurs during the first month of therapy.[12,13] Similarly, NSAID induced derangement of renal hemodynamics usually causes an acute drop in glomerular filtration rate (GFR).

H. Study Procedures

Each patient who completes the trial will undergo, several colonoscopies and sigmoidoscopies. They will be carried out following the guidelines established by the American College of Gastroenterology.

I. Study Data

All blood and serum measurements will be done locally at each medical center. Biopsy results after being evaluated locally will be sent to a central pathology lab, where each specimen will be independently, and blindly evaluated by two pathologists. Any discrepancy will be resolved by a panel of pathologists. During each sigmoidoscopy and colonoscopy the gastroenterologist will record the number and size of polyps. The-endoscopic pictures from approximately 4% of the cases will be randomly selected and reviewed by two gastroenterologists.

J. Analyses

a. Primary Analyses
The primary analysis will be to determine, by the chi square test, whether there is a significant difference between the sulindac and placebo groups in the development of colorectal cancer. Similarly, a difference in the rate of adenomatous disease will be assessed in the subgroup of patients whom at randomization did not have colonoscopy evidence of adenomas.

K. Precautions
The greatest adverse risks associated with this study, are NSAID associated gastrointestinal bleeding (GIB) and acute renal failure. The run in period is designed to identify those people in whom sulindac would be poorly tolerated or even dangerous. In this way, during the run in period the patient will have multiple evaluations for decreased GFR and evidence of GIB. Following randomization the patients will have yearly evaluations by a physician, and serial hemoglobin and creatinines every six months.

L. Projected Benefits

Previous studies suggest that there could be as high as a 40-50% decrease in the incidence of colon cancer and adenoma formation. Among the 5,000 patients which we hope to have complete the treatment arm of the study, we would predict a decrease in the number of colorectal cancers from 85 to 50 and patients with adenomatous disease from 2500 to 1500.

M. Signif icance

Colorectal cancer represents a major health problem in the United States and the cause of death in approximately 65,000 people. Recent studies suggest that NSAID's might have a powerful role in decreasing the incidence and mortality of colorectal cancer. If sulindac could reduce the cancer mortality by even 20% that would lead to 13,000 fewer cancer deaths each year.

N. References

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