NCI, DCPC
Chemoprevention Branch and Agent Development Committee

CLINICAL DEVELOPMENT PLAN:

SULINDAC

DRUG IDENTIFICATION

CAS Registry No.: 38194-50-2

CAS Name (9CI): (Z)-5-Fluoro-2-methyl-1-((4-(methylsulfinyl)phenyl)methylene)-1*H*-indene-3-acetic Acid

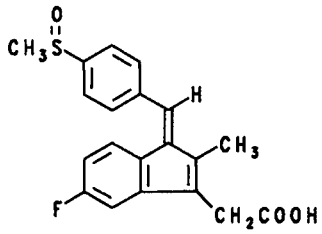
Synonyms: Clinoril® (Active Ingredient)

Related Compounds:

Sulindac Sulfone
(Z)-5-Fluoro-2-methyl-1-((4-methylsulfonyl)phenylmethylene)-1*H*-indene-3-acetic Acid
FGN-1

Sulindac Sulfide
(Z)-5-Fluoro-2-methyl-1-(*p*-methylthiobenzylidene)-3-indenylacetic Acid

Structure:



EXECUTIVE SUMMARY

Sulindac is an FDA-approved non-steroidal anti-inflammatory (NSAID), antipyretic, and analgesic. As with the other NSAIDs currently being considered by the CB for further development (aspirin, ibuprofen, and piroxicam), sulindac derives its activity from inhibition of cyclooxygenase [1,2]. It was discovered in a search for a less toxic version of indomethacin, a structurally related compound. Sulindac is indicated for acute and long-term treatment of the symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, shoulder bursitis/tendinitis, and acute gouty arthritis at doses of 200 to 400 mg qd (*ca.* 0.008–0.016 mmol/kg-bw qd) [2]. In case studies, sulindac seemed effective in pre-

vention or regression of colonic adenomatous polyps in patients with Gardner's syndrome or familial adenomatous polyposis (FAP) at doses from 150 to 400 mg qd. In published studies in experimental animals, the drug inhibited adenomatous polyps and adenocarcinomas in the same tissue. For these reasons, development of sulindac as a cancer chemopreventive drug was undertaken.

Sulindac is actually a sulfoxide prodrug; the hepatic sulfide metabolite is an active NSAID with analgesic and antiinflammatory properties. Plasma levels of sulindac sulfide are sustained approximately twice as long as the parent drug due to enterohepatic circulation and reversible metabolism between the two compounds; this produces a prolonged antiinflammatory effect. Sulindac sulfone, the second major hepatic metabolite, has even more extended plasma levels (3-fold) than the parent drug; however, it lacks antiinflammatory activities.

In preclinical efficacy studies, sulindac inhibited rat and mouse colon, and mouse bladder, lung, and forestomach tumorigenesis. The drug decreased the incidence and multiplicity of premalignant lesions in three of these tissues—colon, forestomach and lung. These results are adequate to support clinical development of sulindac. The CB is funding additional studies in rat mammary gland and colon cancer models. Limited published data suggest that sulindac sulfone also inhibited both premalignant and malignant lesions in the rat colon, but without affecting mucosal prostaglandin (PG) synthesis. This suggests that this metabolite has a chemopreventive activity separate from the antiinflammatory properties of sulindac.

A significant aspect of the development of cancer chemopreventive drugs is to identify and validate intermediate biomarkers. As mentioned above, both sulindac and sulindac sulfone have been shown to inhibit the appearance of histological/premalignant biomarkers. Modulation of other types of biomarkers will be correlated with the latter in studies of sulindac in progress. For example, oncogene and tumor suppressor expression, oncogene mutations, and proliferation markers will be investigated in the carcinogen-exposed rat colon.

Preclinical and clinical safety data were developed by Merck, Sharp & Dohme for NDA approval of sulindac as an antiinflammatory drug. On that basis, no additional preclinical toxicity studies are considered necessary for the prodrug, at least through Phase II trials. Some toxicity studies of the sulfone metabolite may be required.

Most of the therapeutic and toxic effects of sulindac can be related to inhibition of PG synthesis. In published information, moderate gastrointestinal (GI; *e.g.*, nausea, dyspepsia, pain, cramps, diarrhea), hepatic, CNS (*e.g.*, dizziness, headaches), and dermal (*e.g.*, urticaria, pruritis, photosensitivity) reactions are common with human sulindac use, although the incidence is lower than with indomethacin or aspirin. However, the risk for developing GI bleeding and peptic ulcerations appears to be higher for sulindac than for aspirin, ibuprofen or piroxicam. More severe GI or liver toxicity occurs in 1% of patients. Renal function is affected less than with other NSAIDs.

Sulindac is well absorbed, with peak plasma levels occurring within one hour. The primary route of excretion (50%) is the urine, with the majority as sulindac sulfone. A smaller proportion of the dose (25%) appears in the feces as both the sulfone and sulfide metabolites. This pattern agrees with the difference in potency of sulindac and sulindac sulfone as colon cancer chemopreventive agents. Compared to sulindac, a five-fold higher dose of the sulfone metabolite is required to inhibit rat colon carcinogenesis since only one mechanism is available. Fecal excretion of sulindac as both metabolites also takes advantage of PG effects.

NCI has funded two Phase II and one Phase III cancer chemoprevention trials. The completed Phase II trial (Dr. F.M. Giardiello, Johns Hopkins University) in FAP patients given 150 mg sulindac bid for nine months demonstrated a mean decrease in polyp number to 44% of baseline and a mean reduction in polyp diameter to 35% of baseline. No case had complete resolution of all polyps. During the three-month follow-up, polyp size and incidence increased, but remained significantly lower than baseline. Although the effect of sulindac was incomplete, case reports of efficacy in FAP patients were confirmed under the conditions of a controlled clinical trial. It is possible that sulindac could be approved for prevention of colon cancer in FAP patients as an orphan drug. FAP contributes to only 1% (*ca.* 25,000) of new colon cancer cases compared with 5% for hereditary nonpolyposis colorectal cancer (HNPCC) and 94% for sporadic cases.

At this time, it is unknown if sulindac is useful in other populations at high risk for colon cancer, such as HNPCC or sporadic adenomatous polyp patients. The second ongoing NCI-sponsored Phase II trial (Dr. J.A. DiSario, University of Utah Medical Center) is addressing this question in sporadic polyp patients. The effect of two dose levels

of sulindac (150 mg qd and bid) on regression of colonoscopic-proven polyps as well as modulation of other types of intermediate biomarkers (PCNA, whole crypt mitotic count) will be evaluated after one year. Mucosal PGE_2 in the colon is also under investigation as a potential drug effect measurement. Finally, a Phase III trial (Dr. C.L. Loprinzi, Mayo Clinic) is in progress to evaluate the recurrence rate of colorectal polyps in patients with a history of multiple polyposis after three years of sulindac treatment (150 mg bid).

Although other NSAIDs (aspirin, piroxicam, and ibuprofen) are already in various stages of development as cancer chemopreventive drugs, sulindac was also considered due to the presumed lower GI toxicity and the possibility of dissociating the anti-inflammatory activities from other potential chemopreventive mechanisms. Decisions regarding further development of sulindac itself will be delayed until completion of the existing clinical trials. In the interim, however, development of sulindac sulfone as a colon cancer chemopreventive drug will begin. A Phase II trial of the metabolite in a cohort of relatives of "sporadic" colon polyp or cancer patients is under consideration by the CB for 1995. No supply problems are anticipated for either sulindac or sulindac sulfone.

PRECLINICAL EFFICACY STUDIES

In the completed *in vivo* efficacy study sponsored by the CB, sulindac (200–400 mg/kg-bw/day, or 0.56–1.12 mmol/kg-bw/day) demonstrated che-mopreventive activity in the OH-BBN-induced mouse bladder carcinogenesis model [3]. Further evidence of the efficacy of sulindac comes from published studies reporting inhibition of new carcinoma induction [4,5] as well as the growth of existing carcinomas in the DMH-exposed mouse colon [4]. Interestingly, the drug was effective when given simultaneously with the carcinogen, but not when begun 10 days after the first initiating dose. In the rat, inhibition of AOM-induced adenomas and carcinomas by the drug (0.04% of diet, or *ca.* 0.056 mmol/kg-bw/day) was accompanied by decreased PGE_2 synthesis in the colon [6]. The results of animal efficacy studies are adequate to support the clinical development of sulindac. CB-sponsored evaluations of sulindac are in progress in the AOM-induced rat colon and MNU-induced rat mammary gland models of carcinogenesis.

A significant effort in the CB program is to identify and validate intermediate biomarkers of cancer, and evaluate the potential for chemopreventive agents to modulate these markers [7]. Sulindac (400 mg/kg diet, or *ca.* 0.056 mmol/kg-bw/day) added to the diet beginning one week before the carcinogen has demonstrated activity against a putative histological intermediate biomarker of colon cancer in AOM-induced rats—foci of aberrant crypts, especially hexosaminidase-negative foci [8]. Published studies have reported modulation of premalignant lesions in DMH-induced mouse models of carcinogenesis, *e.g.*, colon (adenoma, papilloma) [5,9], lung (adenoma, papilloma) [10–12], and forestomach (papilloma) [11]. However, the effect of dietary sulindac on proliferation biomarkers has shown mixed results. When measured as the proportion of metaphase-arrested cells following vincristine treatment (ip), proliferation was significantly less in colonic adenomas of DMH-exposed mice treated with sulindac than in carcinogen controls [9]. In contrast, doses of the drug that inhibited AOM-induced rat colon carcinogenesis did not affect the proliferation rate in tumors or normal-appearing mucosa when assessed by BrdU labeling index [13]. In ongoing CB studies, effects on additional biomarkers will be correlated with modulation of AOM-induced aberrant crypts, including oncogene and tumor suppressor expression (*myc*, Rb, p53), oncogene mutations (*ras*, p53), and proliferation (PCNA). In addition, other putative histological biomarkers will be monitored (GST-π- and GGT-positive foci, mucin-negative foci).

Limited published information reported that the sulfone metabolite of sulindac also significantly inhibited AOM-induced colon tumorigenesis in the rat [6,13]. Higher doses of the sulfone (0.2% in diet) than sulindac (0.04% in diet) were required to decrease adenoma and carcinoma multiplicity. The mechanism is unknown; no effect on BrdU incorporation was observed after ingestion of either compound [13]. Sulindac sulfone also did not inhibit colonic PGE_2 synthesis [6], although this was assumed to be the mechanism by which NSAIDs prevent cancer.

Other chemoprevention-related activities of the parent drug and the two major metabolites have been characterized *in vitro*. The IC_{50}s for growth inhibition of human colon cancer Ht-29 cells were sulindac, 318 μM; sulindac sulfide, 64 μM; and sulindac sulfone, 119 μM [14]. Although the sulfone does not inhibit PG synthesis, it had half the antiproliferative effect of the sulindac sulfide, the antiinflammatory metabolite of the prodrug. This suggests that other antipromotional mechanisms

may contribute to the chemopreventive effects of sulindac, such as alterations in signal transduction, modulation of enzyme activities (*e.g.*, phosphodiesterase, folate-dependent), inhibition of cyclooxygenase co-oxidation of procarcinogens, or enhancement of immune response.

PRECLINICAL SAFETY STUDIES

Safety No preclinical toxicology or pharmacokinetic studies of sulindac are planned by the CB. Preclinical and clinical safety data were developed by Merck, Sharp & Dohme for NDA approval of sulindac as an antiinflammatory drug. On that basis, no additional preclinical toxicity studies are considered necessary for the prodrug, at least through Phase II trials. Some toxicity studies of the sulfone metabolite may be required.

The short-term TD_{50}s for intestinal ulceration and perforation in rats are 27.4 and 71 mg/kg-bw (0.08 and 0.2 mmol/kg-bw), respectively [reviewed in 15]. In a published study, rats given split daily doses of sulindac ig (0.28 mmol/kg-bw/day) for four days at 17.5 times the maximum human daily dose developed many medium and severe GI ulcerations with some evidence of perforations [16]. In 90-day studies, rats given doses of 40 mg/kg-bw/day (0.11 mmol/kg-bw/day) displayed ulcerative enteritis [reviewed in 15]. Dogs displayed hepatic changes at 20 mg/kg-bw/day, but without concomitant GI ulcerations. Microscopic examination revealed portal fibrosis, bile duct proliferation and inflammatory cell infiltration. Monkeys also lacked evidence of GI ulceration; however, hepatic effects similar to dogs were obtained.

In published reproductive toxicity results, doses equivalent to 2.5–5 times the maximum daily human dose (400 mg qd) decreased the average fetal weight and increased dead pup incidence in rats [2]. Like other NSAIDs, a known effect of sulindac is closure of the ductus arteriosus in female rats treated on gestation day 21 [17]. In mice, cleft palate was obtained in 25% of the litter after a single injection (im) equivalent to the median recommended human daily dose (300 mg qd) given on gestation day 13.5 [18]. *In vitro*, incomplete fusion of explanted palatal processes exposed to sulindac in the culture medium was also obtained.

ADME After oral ingestion, large differences were found among animal species in plasma concentrations of sulindac and its metabolites [reviewed in 15,19]. The values were much higher in rats than in dogs and monkeys. For example, two hrs after a single dose of 10 mg/kg-bw, the plasma concentration of radiolabeled drug plus metabolites was 44 μg/ml in rats compared with only 0.8 μg/ml in dogs, a 50-fold difference [19]. The major metabolites of sulindac are the sulfide and the sulfone; all three compounds accounted for the plasma radioactivity. In rats, the plasma $t_{½}$s for the sulfide (12 hrs) and sulfone (18 hrs) metabolites are longer than that of sulindac (6 hrs). Radiolabeled drug was widely distributed to rat tissues, especially liver, stomach, kidney, and small intestine [19].

The excretion pattern was also highly variable between species. Rats and dogs eliminated sulindac almost exclusively in the feces. Sulindac (25%) and the sulfone metabolite (60%) accounted for most of the fecal radioactivity in rats. In rats and dogs, 52.9% and 92.9% of an oral radiolabeled dose appeared in the bile, respectively. In contrast, urinary excretion predominated in the monkey and human. In the monkey, free and conjugated sulindac were the major sources of urinary radioactivity. As in humans, only trace amounts of the sulfide metabolite are detected in the urine of dog, rat, rabbit, guinea pig and monkey.

CLINICAL SAFETY: PHASE I/II STUDIES

No Phase I trials have been sponsored by the CB because of sufficient testing performed by Merck, Sharp & Dohme. In the completed NCI-sponsored Phase II trial (Dr. F.M. Giardiello), treatment with 300 mg qd for nine months produced no significant effects on hematological parameters or liver and kidney function tests. Most of the following discussion regarding safety and pharmacokinetics of sulindac is drawn from the large amount of published clinical and post-marketing surveillance data.

Drug Effect Measurement Colonic mucosal PGE_2 is being evaluated as a drug effect marker for sulindac in the NCI-funded Phase II trial in progress (Dr. J.A. DiSario). One published study demonstrated decreases of 68% and 52% for PGE_2 and 6-keto-$PGF_{1\alpha}$, respectively, in sigmoid colon mucosa taken from seven patients on six months of sulindac therapy (200 mg bid) [20]. A similar reduction was observed in PG levels in polyp biopsies. If the sulfone metabolite is developed, a more relevant drug effect measurement would need to be identified; the sulfone does not inhibit cyclooxygenase [15]. Based on the metabolism of sulindac, measurement of the a urinary sulfone conjugate may be a possibility.

Safety Most of the adverse effects reported for sulindac can be related to inhibition of PG synthesis. Moderate GI symptoms were most frequent (15–25% of patients), including pain and cramps, dyspepsia, nausea, diarrhea, and anorexia, but at incidences less than with aspirin [2,21–23]. These responses appear to be the result of systemic blockade of PG synthesis alone rather than a combination of systemic and direct action on the upper GI mucosa, since the prodrug requires conversion to the active metabolite in the liver [21]. Inhibition of PGs decreases gastric mucus and bicarbonate production and submucosal blood flow [23]. Peptic ulceration and GI bleeding incidences are higher with sulindac than with ibuprofen, indomethacin, naproxen and tolmetin, but occur only after 3–6 months of treatment [24,25]. However, sulindac had no appreciable effect on platelet function [2].

Moderate dermatological reactions (urticaria, exanthema, pruritus, photosensitivity), and CNS symptoms (dizziness, headache) are common [2].

Renal function appears to be affected less than with other NSAIDs. Even at high doses, glomerular filtration rate is unaltered in patients with chronic renal disease [26]. Many studies suggest that sulindac spares renal function due to its failure to inhibit renal PG synthesis at doses which are effective on extrarenal cyclooxygenase, although this has not been completely proven [21,27–29]. Sulindac is present in the urine primarily as biologically inactive forms (see ADME), so it may affect renal function less than other NSAIDs. As with other NSAIDs, abnormal liver function tests may occur in up to 25% of patients; however, meaningful (3-fold) elevations of enzymes occurred in less than 1% [2]. When hepatocellular injury is seen, it is most often the result of an idiosyncratic reaction. Other idiosyncratic reactions unrelated to inhibition of PG synthesis include pancreatitis, anemia, pulmonary infiltrates, and epidermal necrolysis. These reactions occur infrequently, but are sometimes fatal.

ADME Sulindac is approximately 90% absorbed in humans after oral administration, with peak plasma levels occurring within one hour [reviewed in 2,30,31]. The sulfoxide drug is metabolized in the liver to two major metabolites, the sulfide and the sulfone. The sulfide metabolite is an active NSAID with analgesic and antiinflammatory properties, which the sulfone metabolite lacks. After 200 mg qd or bid, the mean plasma $t_{1/2}$ of sulindac is 7.0 hrs, with >90% serum albumin binding. The mean plasma $t_{1/2}$ of the sulfide metabolite is 18.2 hrs due to reversible metabolism from sulindac and enterohepatic circulation [2,31]. In a small study of a single 300 mg sulindac dose, the sulfone $t_{1/2}$=22.5 hr, and the AUC for the three compounds are: sulindac, 9.3 hr·kg/L; sulindac sulfone, 15.7 hr·kg/L; and sulindac sulfide, 25.4 hr·kg/L [32]. Sustained plasma levels of the sulfide metabolite are consistent with a prolonged anti-inflammatory action.

The primary route of excretion in humans is via the urine as both sulindac and its sulfone metabolite (free and glucuronide conjugates) [2]. Approximately 50% of the administered dose is excreted in the urine, with the conjugated sulfone metabolite accounting for the major portion (28%) [16]. Less than 1% of the administered dose of sulindac appears in the urine as the sulfide metabolite [2]. Biliary excretion and enterohepatic circulation appear to be extensive for the parent and the sulfide [reviewed in 32]. Reabsorption of sulindac from the gastrointestinal tract has been noted 10–12 hours after dosing. Approximately 25% of the dose is found in the feces, primarily as the sulfone (10%) and sulfide (10%) metabolites [2].

CLINICAL EFFICACY: PHASE II/III STUDIES

NCI has funded two Phase II trials and one Phase III trial. The status of these studies is reported in Table I. The completed Phase II trial in FAP patients (Dr. F. M. Giardiello) given 150 mg bid for nine months demonstrated a mean decrease in polyp number to 44% of baseline and a mean reduction in polyp diameter to 35% of baseline [33]. No case had complete resolution of all polyps. During the three-month follow-up, polyp size and incidence increased, but remained significantly lower than baseline. Although the effect of sulindac was incomplete, case reports of efficacy in FAP patients were confirmed under the conditions of a controlled clinical trial. The agent might be useful in hereditary nonpolyposis colorectal cancer or sporadic adenoma patients; this is being investigated in an ongoing Phase II trial (see below).

A second NCI-sponsored Phase II trial (Dr. J. A. DiSario) is evaluating the effect of two dose levels of sulindac (150 mg qd and bid) on adenomatous polyp regression in patients with sporadic, colonoscopic-proven lesions [34]. Modulation of other types of intermediate biomarkers is also included, such as PCNA and whole crypt mitotic count. Mucosal PGE_2 in the colon is being evaluated as a potential drug effect measurement. A Phase III trial (Dr. L.C. Loprinzi) is in progress to evaluate the recurrence rate of colorectal polyps in patients with

a history of multiple polyposis who have had five polyps excised within the prior 12 months [34]. This is a long-term study of the efficacy of three years of sulindac treatment (150 mg bid).

Three studies of sulindac therapy for polyps in FAP patients have been published. The first is a small randomized, placebo-controlled trial which assessed duodenal and rectal polyp regression and mucosal cell proliferation in FAP patients (n=24) who had undergone colectomy and had advanced duodenal polyposis [35]. After six months of treatment with 200 mg sulindac bid, the size of existing rectal polyps decreased significantly as measured subjectively in blinded rectoscopy videotapes; the trend in duodenal polyp size in videotaped duodenoscopies was not significant. Cell proliferation measured as BrdU labeling in biopsies from normal-appearing mucosa decreased significantly in both the duodenum and rectum following sulindac treatment. In a second non-randomized study, treatment with 100 mg sulindac bid for 60 days was assessed in a FAP cohort with (n=6) and without colectomy/ileorectal anastomosis (n=14) [36]. The number of rectal polyps decreased dramatically in all patients, although the average size did not. In contrast, mean proliferation in the rectal mucosa was unaffected by sulindac treatment, since this measurement increased in some patients and decreased in others. Finally, doses of sulindac delivered in suppositories were investigated in a small non-randomized, placebo-controlled study of FAP patients with rectal polyps following colectomy/ileorectal anastamosis [37]. After 300 mg daily for six weeks, 80% (12/15) had partial or complete response. The dose was reduced at intervals; after 42 weeks, two-thirds of the patients showed complete remission (at 25–50 mg daily), while the rest had partial remission (50–100 mg daily). No polyp regression occurred in the placebo group.

Sulindac has been reported to cause the regression of existing colonic polyps and the prevention of new polyps in individual case studies of 22 patients with FAP or Gardner's syndrome, many of whom were related [38–46]. Dosage and treatment regimens varied from 150 to 400 mg sulindac daily for 3–92 months. In one study of 11 patients followed for an average of 4.6 years, most of the polyps disappeared within 6–12 months, and no colorectal cancers appeared after follow-up for 21–92 months [41]. Residual polyps were small and flat, with histological characteristics of benign adenomatous overgrowth. Combining two additional studies, discontinuation of therapy resulted in the return of polyps in seven patients (n=10); with reinstitution of treatment, polyps regressed in six patients [42,43]. It should be noted that clinical efficacy of sulindac in HNPCC or sporadic polyp patients has not been reported. The latter two groups contribute to 99% of new colon cancer cases [46]. Sulindac may be developed for chemoprevention in FAP patients as an orphan drug.

PHARMACODYNAMICS

In the AOM-induced rat model, 0.04% sulindac in the diet (*ca.* 0.056 mmol/kg-bw/day) significantly reduced colon tumors, suggesting that the median human therapeutic dose of 300 mg qd (0.012 mmol/kg-bw/day) is approximately five-fold lower than an effective chemopreventive dose. In contrast, the doses are similar when normalized to surface area: 0.34 mmol/m^2 in rats and 0.49 mmol/m^2 in humans. However, doses between the two species may not be directly equivalent due to the differences in pharmacokinetics. In the rat, 86% of the total dose (25% as sulindac) is excreted in the feces, while humans excrete only 25% by this route (1% as prodrug, 10% as the sulfide) [15,16]. The majority (48%) of a clinical dose is excreted in the urine, decreasing the exposure of the colon. If the sulfide is assumed to be the active form, the difference between the two species in the proportion of the drug excreted in the feces suggests that inhibition of colon cancer in the rat may overestimate efficacy in clinical trials.

If the sulfone metabolite contributes to the chemopreventive efficacy of sulindac in the colon, the rat model still does not serve as a useful pharmacokinetic model. In the rat, sulindac sulfone represents 60% of the dose appearing in the feces, or 52% of the total sulindac dose. In humans, approximately 22% of an oral dose of sulindac reaches the colon as equal proportions of sulindac sulfone and the prodrug; the latter is completely reduced to the sulfide by bacterial microflora.

Inhibition of colon cancer by sulindac appears to involve different mechanisms contributed by the sulfide and sulfone metabolites. In the AOM-induced rat colon model, higher dietary levels of sulindac sulfone (2 g/kg diet, or *ca.* 0.28 mmol/kg-bw/day) than sulindac (400 mg/kg diet, or *ca.* 0.06 mmol/kg-bw/day) were necessary to obtain equivalent inhibition of colon carcinogenesis [6,13]. Although neither agent decreased the colon mucosal proliferation rate [13], sulindac (as the sulfide) inhibited colonic PGE_2 synthesis [6]. The additional

mechanism by which the sulfone metabolite contributes to the chemopreventive effect needs to be ascertained and related to the level of drugs in the colon.

In mice, the sulindac dose required for chemoprevention of bladder cancer (200 mg/kg diet, or *ca.* 0.073 mmol/kg-bw/day) is 5-fold higher than the effective dose for colon cancer (0.014 mmol/kg-bw/day). Assuming mice eliminate sulindac in a manner similar to rats, only 10% of the dose appears in the urine. In humans, approximately half of the sulindac dose is excreted via the urine—20% as the prodrug and 28% as the sulfone metabolite. Since more of the dose appears in the bladder, clinical trials evaluating chemopreventive efficacy appear to be the most promising in this organ.

In the NCI-sponsored Phase II trial in progress in patients with colorectal polyps, plasma sulindac levels are being followed, but not levels of the metabolites. Since the chemopreventive effect often wanes with chronic administration, it is of interest to determine whether metabolism or pharmacokinetics of the prodrug changes over time. Measurement of drug metabolite levels in colonic samples is of greatest value; however, patient accrual is a factor.

PROPOSED STRATEGY FOR CLINICAL DEVELOPMENT

Drug Effect Measurement Issues

Measurement of plasma sulfide is an indication that sulindac is being metabolized by the liver; however, extensive enterohepatic circulation appears to reduce the exposure of the intestines. This metabolite inhibits cyclooxygenase, so tissue PGE_2 may be a useful drug effect measurement for sulindac. However, development of the sulfone metabolite will require an alternate measurement and a sensitive, valid assay. A possibility is determination of sulfone conjugates in urine.

Safety Issues

The critical issue for chronic administration of sulindac is high risk for GI bleeding and peptic ulceration, which is greater than that for ibuprofen and other NSAIDs. The sulfone metabolite may not pose this risk because of the lack of cyclooxygenase inhibition. A comparison of the potential for adverse GI and other effects between sulindac and the sulfone metabolite should be performed.

Pharmacodynamics Issues

The efficacy demonstrated in the rat and mouse colon models may be due to the high colorectal concentrations compared with humans; 86% of the total sulindac dose appears in the feces of rats. In contrast, gastric absorption in humans and primates is high and the principal route of elimination is the urine. Therefore, alternate oral formulations to decrease systemic bioavailability or suppository formulations for rectal administration may need evaluation.

The effectiveness of sulindac in causing regression of existing adenomatous polyps and decreased polyp number appears to wane with chronic administration. A possible alteration in the metabolism and pharmacokinetics of the parent and the metabolites needs to be determined. Also, the mechanism of the chemopreventive effect of the sulfone metabolite, when ascertained, needs to be correlated with the pharmacokinetics of the drug metabolite in the plasma and colon.

Regulatory Issues

Preclinical and clinical safety data and information published by Merck, Sharp & Dohme and human data from long-term analgesic use are available to support NCI trials. On that basis, no additional preclinical toxicity studies are considered necessary, at least through Phase II trials. If further development of the sulfone metabolite is undertaken, some additional carcinogenicity and reproductive preclinical toxicology studies may need to be sponsored.

Intermediate Biomarker Issues

Sulindac has been shown to modulate premalignant lesions in preclinical and clinical studies, especially in the colon. As noted in the clinical development plans for aspirin, ibuprofen and piroxicam, effects on PG synthesis in the colon do not always correlate with decreased proliferation or tumor formation. The influence of NSAIDs on colon carcinogenesis is complex. The response may depend on the identity of the NSAID or carcinogen, the dose employed, or differences in the cell populations sampled. Also, the carcinogenic mechanism related to cyclooxygenase activity in the colon may not be related to a direct effect of the PG end-products. For example, generation of mutagens could be decreased by inhibition of PG synthase-related production of reactive species or

co-oxidation of carcinogens. Other possible mechanisms include altered signal transduction or immune response, or induction of apoptosis. Thus, genetic or differentiation biomarkers should be investigated along with proliferation biomarkers as potential surrogate endpoints for clinical trials of sulindac and sulindac sulfone as a colon chemopreventive agents. This NSAID presents a unique opportunity to differentiate between the cancer inhibitory mechanisms both related and unrelated to PG synthesis.

In order to further develop intermediate biomarkers, additional types need to be identified and validated. To this end, the CB has studies in progress in AOM-induced rat colon (foci of aberrant crypts, enzyme-altered foci, oncogene and tumor suppressor expression, PCNA, oncogene mutations) and in a Phase II trial (polyps, PCNA, whole crypt mitotic counts). These studies may need to be performed with the sulfone metabolite to investigate its chemopreventive mechanism.

Supply and Formulation Issues

Sulindac is available from Merck, Sharp & Dohme and numerous other companies in tablets of 150 and 200 mg by prescription only. Supply does not appear to be a problem; however, a placebo would be required from the manufacturer for any blinded studies. A patent application for sulindac sulfone has been filed. Cell Pathways, Inc., will provide the sulfone metabolite, and no problems are anticipated.

Clinical Studies Issues

Regression of colorectal adenomas by sulindac has been demonstrated clinically, but only in FAP patients or polyp patients with prior colectomies. An ongoing Phase II trial is investigating the efficacy of the drug in a sporadic colon polyp population. No further clinical trials of sulindac will be planned until the results of those in progress have been received.

Sulindac is essentially a prodrug; the sulfide metabolite possesses 2–8 times the NSAID activity of the parent [47–49]. The GI toxicity related to PG synthesis may be ameliorated by treatment with the sulfone metabolite as a substitute. Although this metabolite lacks antiinflammatory activity, it inhibited AOM-induced colonic tumors in the rat by an unknown mechanism. Concomitant development of sulindac sulfone as a colon cancer chemopreventive drug is in the preliminary stages. A Phase II trial of the metabolite in a cohort of relatives of sporadic colon polyp or cancer patients is under consideration for 1995. Pedigree analysis has suggested that inheritance of a partially penetrant autosomal dominant susceptibility gene in 19% of this population increased susceptibility for "sporadic" colon carcinogenesis [50,51].

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Table I. Clinical Trials of Sulindac Sponsored/Funded by NCI, DCPC

Study No. Title (PI) Period of Performance IND No. (Sponsor)	Cancer Target	Study Population No. of Subjects	Dose(s) Study Duration	Endpoints	Remarks
Phase II (Dose titration, efficacy, intermediate biomarkers)					
UO1-CA-53801 Sulindac Chemoprevention in Adenomatous Polyposis Coli (Dr. Francis M. Giardiello, Johns Hopkins University School of Medicine) 3/91–2/93 Investigator IND	Colon	Familial adenomatous polyposis patients 22 patients	Oral 150 mg bid for 9 months, follow-up for 3 months	Efficacy: Polyp number, size of polyps	Study complete Polyp number decreased 56%; polyp size decreased 65%. No cases had complete resolution of polyps. Size and incidence increased during follow-up, but remained significantly lower than baseline Published report: [33]
UO1-CA-56433 Phase II Randomized, Placebo-controlled Trial of Sulindac for Chemoprevention of Premalignant Colorectal Adenomas (Dr. James A. DiSario, University of Utah Medical Center) 9/92–8/96 Investigator IND	Colon	Patients referred for colonoscopy with sporadic left-sided polyps 5–9 mm in diameter 60 patients (20 per arm)	Oral 150 mg qd and bid for 1 year	Efficacy: Incidence of adenoma regression Other intermediate biomarkers: PCNA, whole crypt mitotic count Drug effect measurement: colonic mucosal PGE_2	Efficacy and intermediate biomarker study in progress

Table I. Clinical Trials of Sulindac Sponsored/Funded by NCI, DCPC (*continued*)

Study No. Title (PI) Period of Performance IND No. (Sponsor)	Cancer Target	Study Population No. of Subjects	Dose(s) Study Duration	Endpoints	Remarks
Phase II (Dose titration, efficacy, intermediate biomarkers) *(continued)*					
Planned Study Phase II Trial with Sulindac Sulfone 1995 NCI IND	Colon	Patients with previously resected colorectal polyps	Oral 3 years	Efficacy: New polyps; other intermediate biomarkers	Study not yet designed
Phase III (Efficacy, intermediate biomarkers)					
NCCTG-909251 Randomized Placebo-controlled, Double-blind Study in the Prevention of Colorectal Adenocarcinoma with Sulindac in Patients with Multiple Polyposis (Dr. Charles L. Loprinzi, Mayo Clinic) 1991– Investigator IND	Colon	History of multiple polyposis (>50 colorectal polyps) and colectomy with at least 5 rectal polyps diagnosed and excised *within 12 months prior* to entry 50 patients	Oral 150 mg bid for 3 years	Efficacy: Recurrence of colorectal polyps, latency	Efficacy study in progress

SULINDAC DEVELOPMENT STATUS