NCI, DCPC
Chemoprevention Branch and Agent Development Committee

CLINICAL DEVELOPMENT PLAN:

IBUPROFEN

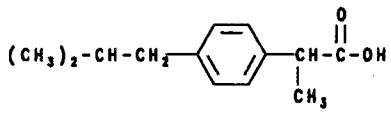
DRUG IDENTIFICATION

CAS Registry No.: 15687-27-1

CAS Name (9CI): α-Methyl-4-(2-methylpropyl)benzeneacetic Acid

Synonyms: Advil® (Active Ingredient)
Brufen
2-(4-Isobutylphenyl)propionic Acid
Midol 1200® (Active Ingredient)
Motrin® (Active Ingredient)
Nuprin® (Active Ingredient)

Structure:



EXECUTIVE SUMMARY

Ibuprofen is a nonsteroidal antiinflammatory (NSAID) [1,2], antipyretic and analgesic approved for both prescription and over-the-counter (OTC) use [3]. The drug is indicated for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis, relief of mild to moderate pain or fever, and treatment of primary dysmenorrhea. The suggested therapeutic dose range is 1,200–3,200 mg daily (*ca.* 0.08–0.22 mmol/kg-bw). The activity of ibuprofen is derived primarily from competitive inhibition of cyclooxygenase [4–7]; however, the drug's full effects are incompletely understood. It may also have other potential chemopreventive activities, including antiproliferation [8] and free-radical scavenging [9]. Ibuprofen has demonstrated chemopreventive activity in several animal cancer models, including rat colon and mammary glands, mouse bladder, and hamster buccal pouch. In addition, epidemiological studies have associated non-aspirin NSAID use with decreased risk for colorectal polyps [10] and cancer [11]. Finally, the gastrointestinal (GI) toxicity of ibuprofen in humans appears to be less than other NSAIDs under consideration as chemopreventive agents (aspirin, piroxicam, and sulindac). For these reasons, development of this drug as a cancer chemopreventive agent was undertaken by the CB.

Existing preclinical efficacy studies are adequate to support clinical development of ibuprofen. Identification and validation of intermediate biomarkers

is an important aspect of drug development. Besides efficacy in animal cancer models, modulation of histological intermediate biomarkers by ibuprofen has been demonstrated in the rat colon (aberrant crypt foci) and mouse lung (papilloma) and forestomach (papilloma). Evaluation of other types of biomarkers is in progress in CB-sponsored studies in the rat colon, including genetic (*myc*, Rb and p53 expression, *ras* and p53 mutations), proliferation-related (PCNA) and putative histological/premalignant lesions (GST-π- and GGT-positive foci, hexosaminidase- and mucin-negative foci).

All preclinical and clinical safety and efficacy information used by the FDA for NDA approval of ibuprofen is available to support CB development of the drug as a cancer chemopreventive. On that basis, no additional preclinical studies are considered necessary to support clinical development, at least through Phase II trials.

A CB-funded Phase I trial of ibuprofen is in progress in patients who have had at least one adenomatous colon polyp removed. The first step, a dose-escalation study using three single dose levels—75, 200, and 800 mg—for investigation of pharmacokinetics and safety, has been completed. In the second dose-titration step, patients will be evaluated for rectal mucosal prostaglandin (PGE_2) and drug levels after one month of treatment with 0, 300, and 600 mg ibuprofen daily. The dose that produces a 50% decrease in PGE_2 without significant toxicity will be used in a future Phase II trial.

Bladder and colon cancers will be evaluated as targets for chemoprevention by ibuprofen because of demonstrated preclinical efficacy in these tissues and excretion of the drug primarily in the urine in experimental animals and humans. Two Phase II trials are under consideration for 1995. One trial is planned in patients with prior resected bladder cancer, subsequently treated intravesically with BCG. A second trial evaluating regression of colon polyps has been proposed.

Ibuprofen is available as an OTC drug or by prescription from several pharmaceutical companies. For future blinded studies, it will be necessary to obtain an identical placebo.

PRECLINICAL EFFICACY STUDIES

In studies sponsored by the CB, ibuprofen has demonstrated chemopreventive efficacy in several animal carcinogenesis models. It inhibited AOM-induced colon adenocarcinomas (400 ppm in diet, or *ca.* 0.1 mmol/kg-bw/day) [12] and MNU-induced mammary gland tumors in rats (250 mg/kg diet, or *ca.* 0.06 mmol/kg-bw/day), and OH-BBN-induced bladder tumors in mice (250–500 mg/kg diet, or *ca.* 0.16–0.32 mmol/kg-bw/day). Further evidence of the chemopreventive efficacy of ibuprofen comes from published studies reporting inhibition of cancer in rat mammary glands (1,000–2,000 mg/kg diet, or *ca.* 0.24–0.48 mmol/kg-bw/day) [13], mouse lung (263 mg/kg diet, or *ca.* 0.15 mmol/kg-bw/day) [14], and hamster buccal pouch (1.5 mg/animal, or 0.007 mol/animal) [15]. The results of animal efficacy studies are adequate to support the clinical development of ibuprofen.

A significant effort in the CB program is to identify and validate intermediate biomarkers of cancer and evaluate potential for chemopreventive agents to modulate these markers. Ibuprofen has demonstrated activity against histological biomarkers (aberrant crypt foci) in the AOM-induced rat colon model of carcinogenesis (200–400 mg/kg diet, or *ca.* 0.03–0.06 mmol/kg-bw/day) [12]. It is currently being studied for its effect on other types of colonic intermediate biomarkers in the same assay, including oncogene and tumor suppressor expression (*myc*, Rb, p53) and mutations (*ras*, p53), and PCNA. Additional putative histological biomarkers will also be monitored (GST-π- and GGT-positive foci, hexosaminidase- and mucin-negative foci). Published studies have demonstrated decreased multiplicity and/or incidence of premalignant lesions in NNK-induced mouse lung (papillomas) and forestomach (papillomas) models of carcinogenesis [16].

PRECLINICAL SAFETY STUDIES

Safety Preclinical and clinical safety information has been generated for approval of ibuprofen as an antiinflammatory drug. On that basis, no additional preclinical studies are considered necessary, at least through Phase II trials.

In a published acute toxicity study, the ibuprofen dose producing gastric ulceration in 50% of rats was 71.5 mg/kg-bw (0.35 mmol/kg-bw) [17]. With chronic dosing for 26 weeks, moderate toxicity occurred at 180 mg/kg-bw/day in rats [18]; this dose is approximately 6 times the median human therapeutic dose. The effects were primarily intestinal damage, anemia, and increased liver and kidney weights. Abnormal kidney histology, including renal papillary necrosis, occurred only at lethal doses. In rabbits, ibuprofen was not teratogenic at toxic doses, but it may decrease fertility [3].

ADME Preclinical and clinical pharmacokinetic information has been generated for approval of ibuprofen as an antiinflammatory drug.

CLINICAL SAFETY: PHASE I STUDIES

The CB is sponsoring a Phase I pharmacokinetic and dose-titration study of ibuprofen (Dr. D.S. Alberts, University of Arizona). In the single dose step, patients received three consecutive single doses (75, 200 and 800 mg on days 1, 8 and 18, respectively); plasma pharmacokinetic parameters are being determined [19]. In the dose-titration step, patients will be evaluated for rectal mucosal PGE_2 levels after one month of treatment with 0, 300, and 600 mg ibuprofen daily. The dose that produces a 50% decrease in PGE_2 without significant toxicity will be used in future Phase II trials. Originally, patients (male and female) between the ages of 55 and 70 who had at least one colonic adenomatous polyp removed could be entered into the trial. The protocol has been amended to include patients of any age with a previously resected polyp(s) within the last seven years (Table I). The informed consent form is being revised to reflect the Step 2 protocol.

Drug Effect Measurement The most obvious drug effect is measurement of prostaglandins (PGs) in platelets or urine. However, PGE_2 production in colonic or rectal mucosa is being evaluated in the Phase I trial of ibuprofen. In an ongoing Phase I trial on aspirin, PGE_2 and $PGF_{2\alpha}$ levels appear to have been successfully measured at several time points in rectal biopsies.

Safety In extensive post-marketing surveillance, ibuprofen has been shown to be one of the safest NSAIDs [20–23]. GI side effects are experienced by 5–15% of patients taking ibuprofen; epigastric pain, nausea, heartburn and sensations of "fullness" in the GI tract are the usual difficulties. However, the incidence of these side effects is less with ibuprofen than with aspirin, indomethacin, piroxicam, or sulindac. Borderline elevations of liver function indicators may occur in up to 15% of patients. These levels may progress on occasion; however, meaningful elevations (3-fold increase over normal) occur in <1% of patients. Other side effects of ibuprofen have been reported less frequently. They include thrombocytopenia, skin rashes, headache, dizziness and blurred vision, and, in a few cases, toxic amblyopia, fluid retention, and edema. Occult blood loss is uncommon.

ADME The pharmacokinetics of ibuprofen are best described by a two-compartment open model with first-order absorption [24,25]. Ibuprofen is rapidly absorbed after oral administration, with serum or plasma t_{max} levels generally attained within 1½–2 hrs [25,26]. The drug is more than 99% bound to plasma proteins, as illustrated by the small V_d (6.35 L). The serum elimination $t_{½}$ is approximately 2 hrs. An apparent linear dose-response relationship exists between the amount of drug administered and the plasma AUC after single doses of 200 and 800 mg. Above 800 mg, however, AUC increases less with dose.

Eighty-four percent (84%) of an ibuprofen dose is recovered in urine, primarily as conjugated hydroxy- and carboxymetabolites; only 1% of a 400 mg dose is excreted unchanged [24–26]. In normal volunteers, the metabolites do not appear in the serum. Ibuprofen pharmacokinetics are only minimally influenced by advanced age, the presence of alcoholic liver disease, or rheumatoid arthritis.

CLINICAL EFFICACY: PHASE II STUDIES

No clinical efficacy studies of ibuprofen have been sponsored so far by the CB. Two Phase II studies are under consideration for 1995—one in a bladder cancer cohort and one in a cohort of patients with colon polyps. In preclinical efficacy studies, ibuprofen inhibited mouse bladder tumors; in both humans and experimental animals (rat, dog, baboon), the majority of the drug is excreted in the urine. Although aspirin and sulindac have already been associated with regression of adenomatous polyps, ibuprofen was also chosen for further study as a colon cancer chemopreventive because of its efficacy in several tissues in preclinical studies and its presumed greater human safety, depending on the administered dose.

PHARMACODYNAMICS

In preclinical studies, the effective dietary dose against AOM-induced rat colon carcinogenesis was 400 ppm (*ca.* 0.1 mmol/kg-bw/day); however, this was the lowest dose tested. This is equivalent to the 26-week NOEL in the same species (0.1 mmol/kg-bw/day) and the lowest therapeutic human dose (1,200 mg ibuprofen daily, or *ca.* 0.08 mmol/kg-bw). It is unknown if lower doses will be effective in Phase II clinical trials.

PROPOSED STRATEGY FOR CLINICAL DEVELOPMENT

Drug Effect Measurement Issues

In preclinical studies in the rat colon, PG synthesis (PGE_2, $PGF_{2\alpha}$) in the mucosa is being evaluated as a drug effect measurement. Measurement of PG synthesis in colonic or rectal mucosa should be considered in the proposed Phase II trial in colon depending on results from the Phase I trial. In a CB-sponsored Phase I trial of aspirin, pencil-tip rectal biopsies for determination of PGE_2 and $PGF_{2\alpha}$ have been obtained success-fully at several time points.

Safety Issues

In extensive pre-registration and post-marketing studies, ibuprofen has been shown to be a safe drug. The fact that the prescribed dosage for ibuprofen has been gradually increased since its introduction in the U.S. in 1974 reflects the relative lack of toxicity. Published clinical studies and case reports indicate that its overall therapeutic benefit-to-risk ratio is equal to or better than those of other available NSAIDs. The most common side effects are GI in origin, usually indigestion and nausea. Serious, but rare, adverse effects include acute renal failure, renal papillary necrosis, and hepa totoxic reactions. Liver function should be monitored on long-term ibuprofen administration.

Pharmacodynamics Issues

It has been suggested that the chemopreventive activity of NSAIDs may be due to effects other than inhibition of PG synthesis. For example, the sulfone metabolite of sulindac, which lacks the antiinflammatory properties of the parent drug, is an effective chemopreventive in the colon. It is unknown if the major urinary metabolites of ibuprofen possess either antiinflammatory or other chemopreventive activities. The relationship between the drug form present in urine and chemopreventive efficacy in the bladder is an important issue in determining the mechanism of ibuprofen.

Information from the Phase I trial of ibuprofen may be helpful when designing the proposed Phase II trial evaluating regression of colorectal polyps. Dr. D.S. Alberts will be correlating rectal mucosa PG levels with dose.

Regulatory Issues

All preclinical and clinical safety data and information used by FDA for NDA approval of ibuprofen is available to support NCI studies without the necessity of formal reference procedures. On that basis, no additional preclinical studies on the drug are considered necessary to support clinical development, at least through Phase II trials.

Intermediate Biomarker Issues

An important aspect of cancer chemopreventive drug development is to identify and validate intermediate biomarkers for use as surrogate trial endpoints. In NCI, DCPC and published reports, ibuprofen has been shown to inhibit putative histological biomarkers in rat colon and mouse lung and forestomach models of carcinogenesis. The NCI now has the drug on test in the AOM-induced rat colon model with modulation of other intermediate biomarkers as the endpoint. The types of biomarkers include genetic (*myc*, Rb and p53 expression; *ras* and p53 mutations), proliferation-related (PCNA) and putative histological/premalignant lesions (GST-π- and GGT-positive foci, hexosaminidase- and mucin-negative foci, aberrant crypt foci). The proposed Phase II trials should include identification and evaluation of intermediate biomarkers in bladder and colon.

Evidence from preclinical studies suggests that other types of intermediate biomarkers should be carefully chosen when assessing the effect of NSAIDs on colon carcinogenesis. For example, changes in proliferation biomarkers do not always correlate with decreases in colon tumor incidence or local PG synthesis. Oral aspirin treatment of either control or DMH-exposed rats decreased colon PGE_2 production by *ca.* 96% [27]. In contrast, the NSAID has no effect on mucosal proliferation (measured as [^{3}H]-thymidine incorporation) in the DMH-induced group even though colon adenocarcinoma incidence significantly decreased. Furthermore, aspirin enhanced colon proliferation in the absence of carcinogen. In a related example, indomethacin had no effect on colon PGE_2 synthesis at a dose which reportedly inhibited colon tumor formation [28]; administration of a stable PGE analog did not neutralize the chemopreventive efficacy of indomethacin [reviewed in 27]. Conversely, numerous reports have demonstrated that PGs can inhibit proliferation of animal and human tumor cells *in vitro* and *in vivo* and rat colon mucosa *in vitro* [reviewed in 7]. Thus, the influence of

NSAIDs on colon carcinogenesis is complex. The response may depend on the identity of the NSAID or carcinogen, or the dose employed. Differences in the cell populations sampled (*e.g.*, scraping of the entire mucosa) may also be a confounding factor; it has been suggested that host cells rather than tumor cells are the major sources of PGs that contribute to colon carcinogenesis [41]. Finally, 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 biomark-ers should be investigated along with proliferation biomarkers as potential surrogate endpoints for clinical trials of ibuprofen as a colon chemopre-ventive agent.

Drug Supply and Formulation Issues

Ibuprofen is available as an OTC drug in 200 mg tablets and by prescription in 400, 600, and 800 mg tablets. An active use patent is held only for a liquid children's formulation. If a particular dose or dosage form is proposed for which no placebo exists, it might be necessary to formulate both ibuprofen and a placebo for a blinded study.

Clinical Studies Issues

Ibuprofen was chosen for further development as a bladder and colon cancer chemopreventive drug because of its wide efficacy and relative safety in preclinical studies. A Phase II trial in a bladder cohort is under consideration for 1995. The drug inhibited mouse bladder tumors in preclinical studies; in humans and experimental animals, the majority of the drug is excreted in the urine. A second Phase II trial in a cohort of patients with resected colon polyps is planned for 1995. Ibuprofen inhibited both premalignant and malignant lesions in animal models of colon carcinogenesis. Although sulindac has been associated with regression of adenomatous polyps in the human colon, ibuprofen appears safer on long-term administration. Finally, ibuprofen has demonstrated greater safety than aspirin and piroxicam; aspirin is already in several colon trials and has been associated with reduced risk of colon cancer in epidemiological studies.

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Table I. Clinical Trials of Ibuprofen 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 I (Safety, ADME)					
NO1-CN-85106-02 Phase I and Pharmacokinetic Studies of Ibuprofen (Dr. David S. Alberts, University of Arizona) 9/90– IND 39,517	—	Patients over 18 years of age with at least 1 prior resected colonic adenomatous polyp(s); stratified by age: 18–65; 66–80 yrs Step 1: 10 patients Step 2: 30–36 patients Step 3: 36 patients	Step 1: Single oral dose escalation: 75, 200, 800 mg Step 2: Oral 0, 300, and 600 mg daily for 1 month. Step 3: Doses selected from step 2 for 6 months (3 doses q8h) 3 years	Step 1: Pharmacokinetics in plasma, buccal mucosa, rectal mucosa; safety Step 2: Dose-titration against rectal drug effect measurement (50% decrease in PGE_2) and drug levels Step 3: Intermediate biomarkers (rectal mucosal cell proliferation)	Step 1 has been completed; the results are being analyzed
Phase II (Dose titration, efficacy, intermediate biomarkers)					
Planned Study Phase IIa/IIb Chemoprevention Study of Ibuprofen 1995 IND 39,517	Bladder	Patients with resected superficial bladder cancer subsequently treated intravesically with BCG		Efficacy: Intermediate biomarkers	Study under consideration
Planned Study Phase II Chemoprevention Study of Ibuprofen 1995 IND 39,517	Colon	Patients with previously resected colorectal adenomatous polyps		Efficacy: Polyp regression; other intermediate biomarkers	Study under consideration

IBUPROFEN DEVELOPMENT STATUS