

Comparative Bioavailability of Sulindac in Capsule and Tablet Formulations

Joel M. Reid,¹ Sumithra J. Mandrekar,¹ Elsa C. Carlson,¹ W. Scott Harmsen,¹
Erin M. Green,¹ Renee M. McGovern,¹ Eva Szabo,² Matthew M. Ames,¹
Daniel Boring,² and Paul J. Limburg¹ for the Cancer Prevention Network

¹Mayo Clinic College of Medicine, Rochester, Minnesota and ²Division of Cancer Prevention, National Cancer Institute, NIH, Bethesda, Maryland

Abstract

The cyclooxygenase (COX)-2 enzyme appears to be an important target for cancer chemoprevention. Given the recent emergence of potentially serious cardiovascular toxicity associated with selective COX-2 inhibitors, nonsteroidal antiinflammatory drugs (NSAIDs), which inhibit both COX-1 and COX-2, have received renewed attention as candidate chemoprevention agents. Sulindac has shown consistent chemopreventive potential in preclinical studies as well as in a limited number of clinical trials reported to date. For the current pharmacokinetic study, sulindac capsules were prepared to facilitate ample agent supplies for future intervention studies. Encapsulation of the parent compound (sulindac sulfoxide) can be readily accomplished, but the effects of alternate formulations on bioavailability have

not been rigorously examined. In the present single-dose, two-period crossover trial, we conducted pharmacokinetic analyses of sulindac in capsule (test) versus tablet (reference) formulations. Overall, bioavailability appeared to be higher for the capsule compared with the tablet formulation based on test-to-reference pharmacokinetic variable ratios for the parent compound alone. However, additional analyses based on the sulfide and sulfone metabolites of sulindac with the same pharmacokinetic variables indicated similar chemopreventive exposures between the capsule and tablet formulations. These data support the use of sulindac capsules, which can be readily prepared with matching placebos, in future blinded chemoprevention trials. (Cancer Epidemiol Biomarkers Prev 2008;17(3):674–9)

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) represent an intriguing class of candidate chemoprevention agents for a variety of epithelial cancers. Since the first case series of colorectal polyp regression mediated by sulindac among familial adenomatous polyposis patients was reported over two decades ago (1), numerous cell culture, animal model, and human observational studies have shown consistent anticancer effects from several different NSAIDs (2). Although the mechanisms of action remain incompletely defined, at least part of the chemopreventive activity appears to be mediated by inhibition of the cyclooxygenase (COX) enzyme. The two main COX isoforms, COX-1 and COX-2, catalyze the conversion of arachidonic acid into prostaglandins and thromboxane. COX-1 is constitutively expressed in most normal tissues, whereas COX-2 expression is stimulated by proinflammatory cytokines, hormones, and other growth-promoting factors (3). NSAID derivatives that selectively inhibit COX-2, such as celecoxib and rofecoxib, have shown substantial efficacy in three large colorectal adenoma chemoprevention trials (4–6), but

these agents have also been associated with increased cardiovascular toxicity (7, 8). Consequently, interest in further investigation of traditional NSAIDs for chemopreventive applications has been recently renewed.

Sulindac is a commercially available, prescription NSAID that is approved in 34 countries (Martindales Extra Pharmacopeia), including the United States. The U.S. Food and Drug Administration has approved sulindac for treating acute gouty arthritis, acute painful shoulder (bursitis/tendonitis), osteoarthritis, and rheumatoid arthritis (<http://www.fda.gov>). In addition to its established anti-inflammatory, antipyretic, and analgesic properties, sulindac is thought to provide anticarcinogenic effects based on extensive data from cell culture experiments and animal model systems as well as more limited data from early-phase chemoprevention trials conducted primarily among adenomatous polyposis patients (9–11). Following ingestion, the parent compound (sulindac sulfoxide) is converted into sulindac sulfide, which appears to be the primary COX-inhibiting metabolite. The second major metabolite, sulindac sulfone (exisulind), has also been shown to interrupt carcinogenesis albeit through COX-independent pathways (12, 13) and has undergone limited clinical development to date given some toxicity concerns (14–16).

As recently noted elsewhere (17), optimizing the use of currently available agents to reduce cancer risk should help to speed the progress of chemoprevention research. However, engaging pharmaceutical partners to invest in this area may be increasingly difficult, particularly for drugs like sulindac that can be marketed generically.

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Requests for reprints: Paul J. Limburg, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. Phone: 507-266-4338; Fax: 507-266-0350. E-mail: limburg.paul@mayo.edu

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To address this potential agent supply barrier, the Division of Cancer Prevention, National Cancer Institute commissioned the preparation of sulindac capsules and matching placebos for investigation in future blinded clinical trials. In the present study, we sought to compare the rate and extent of absorption of sulindac from capsules versus tablets, each at the commonly prescribed dose of 150 mg, to establish sulindac capsules as a pharmaceutical alternative for sulindac tablets.

Materials and Methods

The study was designed as a single-dose, two-period crossover trial and was conducted through the National Cancer Institute-sponsored, multidisciplinary Cancer Prevention Network. All aspects of the trial protocol were reviewed and approved by the Mayo Foundation Institutional Review Board before activation.

Subject Population. All study participants were recruited at a single institution (Mayo Clinic Rochester) and included healthy volunteers (Eastern Cooperative Oncology Group performance status ≤ 2) who were ages ≥ 40 years and had normal organ and bone marrow function, as documented by complete blood counts and routine serum chemistries, at baseline. Women of childbearing potential were required to document a negative pregnancy test before enrollment. Enrolled trial participants were asked to abstain from using NSAIDs (except aspirin ≤ 81 mg/d), selective COX-2 inhibitors, and selected herbal products (Saw Palmetto and St. John's Wort) for the duration of the trial. Subjects were also advised to avoid alcoholic and caffeinated beverages for ≥ 24 h before agent administration and until all venipuncture samples had been obtained. Concomitant medications were recorded at baseline. No subjects reported taking oral contraceptives.

Agent Supplies and Distribution. Sulindac capsules and tablets were provided by the Division of Cancer Prevention, National Cancer Institute. Sulindac capsules (test formulation) were prepared by University Pharmaceuticals of Maryland. Each capsule contained 150 mg sulindac, magnesium stearate, and colloidal silicon dioxide, all USP grade. The percent relative SD for content uniformity of the capsules was 3.6%. Sulindac tablets (reference formulation) were prepared by Watson Pharmaceuticals. Each tablet contained 150 mg sulindac, magnesium stearate, microcrystalline cellulose, starch (corn), and stearic acid, all USP grade. The percent relative SD for the content uniformity of the tablets was 1.0%. Bulk supplies were packaged, labeled, and distributed by Fisher BioServices. Individual doses were repackaged and labeled by experienced pharmacy personnel at the Outpatient Cancer Therapy Drug Preparation Area, Mayo Clinic Rochester. Agents were stored in a secure area at controlled room temperature (20–25°C). Reserve supplies of both formulations were retained for future analyses in accordance with standard regulatory guidelines (21 CFR 320.63). Both capsules and tablets were tested for dissolution using the USP sulindac tablet method and both capsules and tablets had a $Q = 80\%$ within 45 min. Additionally, the difference factor for the two curves was >50 , indicating comparable immediate release profiles for both capsules and tablets

(<http://www.fda.gov/cder/guidance/1713bp1.pdf>; last accessed 8/29/07).

Participants were randomly assigned to one of two sulindac dosing sequences: capsule followed by tablet (arm A) or tablet followed by capsule (arm B) using a 2×2 crossover design. A washout period of 7 to 10 days was included between dosing cycles. Agents were administered with ~ 250 mL water after a fasting period of ≥ 2 h under the supervision of trained personnel in the General Clinical Research Center. Subjects were further instructed to fast for ≥ 1 h following agent ingestion.

Pharmacokinetic Assessments. Sulindac, sulindac sulfide, and exisulind were provided by LKT Laboratories. Indomethacin was used as the internal standard and was purchased from Sigma. OmniSOLV high-performance liquid chromatography-grade methanol, acetonitrile, and water were purchased from EMD Chemicals. Orochem Technologies Protein Crash Plates, 96-well Collection Plates, Cap Mats, Zorbax SB-CN high-performance liquid chromatography columns (4.6 \times 150 mm, 5 μ m), and Brownlee NewGuard RP-18 precolumns (3.2 \times 15 mm, 7 μ m) were purchased from Chrom Tech. Recovered human plasma from healthy volunteers was purchased from the Mayo Clinic Rochester Blood Bank and frozen at -20°C .

Stock solutions of 1.0 mg/mL sulindac and 1.0 mg/mL indomethacin were prepared in 75:25 (v/v) acetonitrile/water in amber borosilicate glass vials. Working standards (20 \times concentrations) were prepared fresh each day by dilution of the primary stock solutions with 75:25 (v/v) acetonitrile/water. Standards were prepared by adding working standard solution to thawed human plasma. Subject, standard, and quality-control samples (0.2 mL of each) were added to each well of a 96-well protein crash plate along with 20 μ L of 50 μ g/mL indomethacin solution. Samples were mixed for 15 s followed by the addition of 0.4 mL acetonitrile to each well to precipitate proteins and then shaken for 20 min at 900 rpm on an Eppendorf Thermomixer R set at 20°C . Samples were filtered into a 96-well collection plate by vacuum using an Empore Vacuum Manifold under 15 to 20 in. Hg vacuum pressure. The filtrate was concentrated to dryness under a gentle stream of nitrogen. The residue was reconstituted in 200 μ L of 1:1 (v/v) acetonitrile/50 mmol/L potassium phosphate buffer (pH 3.0) with shaking for 20 min at 900 rpm on an Eppendorf Thermomixer R set at 20°C . Standard curves were linear ($r^2 > 0.99$) over the specified range with a coefficient of variation for concentration values at the lower limit of quantitation (0.05 μ g/mL) of $<2\%$ and the between-day coefficient of variation for the slope of standard curves of $<6\%$. The between-day coefficients of variation for the quality-control samples were 1.3% to 2.2%.

The high-performance liquid chromatography system consisted of a Shimadzu liquid chromatograph with a SCL-10Avp system controller, SIL-10ADvp autoinjector (injection volume, 20 μ L) fitted for 96-well plates, LC-10ADvp pump (flow rate, 1.0 mL/min), DGU-14A degasser, a FCV-10ALVP low pressure gradient unit, and SPD10-AVvp UV-Visible detector (wavelength, 340 nm). The high-performance liquid chromatography assay was based on two published methods (18, 19). Separation of sulindac, sulindac sulfide, exisulind, and indomethacin was achieved with a Zorbax SB-CN

Table 1. Baseline characteristics, overall and by dosing arm

	Overall	Arm A	Arm B
Subjects, <i>n</i>	24	13	11
Age, mean (SD)	48.3 (6.9)	46.2 (4.41)	50.9 (8.58)
Gender, <i>n</i> (%)			
Female	19 (79.2)	10 (76.9)	9 (81.8)
Race/ethnicity, <i>n</i> (%)			
White	24 (100)	13 (100)	11 (100)
Non-Latino	24 (100)	13 (100)	11 (100)
Body mass index (kg/m ²), mean (SD)	25.9 (5.04)	25.1 (4.00)	26.8 (6.13)

analytical column using a Brownlee NewGuard RP-18 precolumn. Mobile phase was composed of 45:55 (v/v) acetonitrile/50 mmol/L potassium phosphate (pH 3) and delivered isocratically at a flow rate of 1.0 mL/min at ambient temperature. The injection volume was 20 μ L.

Venipuncture samples were obtained for pharmacokinetic analyses at the following time points: 0.25 h before agent administration and 0.25, 0.50, 1.0, 1.5, 2, 3, 4, 6, 8, and 24 (\pm 2) h after agent administration. Noncompartmental analysis was done using WINNONLIN. The terminal elimination rate constant (kel) was calculated by linear least squares regression of the linear terminal elimination phase of the graph of log (plasma concentration) versus time. Area under the concentration-time curve (AUC) was determined by trapezoidal approximation from the start of treatment to the last detectable plasma concentration (C_{last}) with residual area after C_{last} calculated by $AUC_r = C_{last} / kel$. The elimination half-life was calculated by $t_{1/2} = 0.693/kel$.

Statistical Analyses. Primary trial endpoints included comparisons of systemic exposure between the capsule (test) and tablet (reference) formulations for the parent compound as characterized by the maximum observed plasma concentration (C_{max}), time of the maximum plasma concentration (T_{max}), and area under the plasma concentration-time curve (AUC) from ingestion of the oral dose to 8 h ($AUC_{0-8 h}$) or total AUC ($AUC_{0-\infty}$). Secondary endpoints included comparisons of systemic

exposures ($AUC_{0-24 h}$ or $AUC_{0-\infty}$) for the sulfide and sulfone metabolites. Comparability limits were predefined and required that the 90% confidence intervals of the log-transformed data for each of the ratios of the average measures of systemic exposure (population geometric means) fall within 80.00% to 125.00% of each other and that the effect of formulation be not found significant in the ANOVA at a one-sided $\alpha = 0.05$ level of significance. Sample size calculations were based on a total of 24 subjects (12 per dosing arm), which provided 80% power to show comparable bioavailability for the parent compound based on an estimated 15% intersubject variability (20).

Descriptive statistics were used to summarize the baseline subject characteristics and standard graphical techniques were used to present the concentration-time curves for subjects receiving the capsule and tablet formulations. ANOVA models were used to test for significant differences between formulations while accounting for a possible crossover effect. The statistical models included factors accounting for the following sources of variation: intervention arm, subject nested within intervention arm, period, and formulation (21, 22). Estimates for the mean-adjusted differences between intervention arm and the SE associated with these differences were computed to estimate the 90% confidence interval for the test-to-reference ratios of C_{max} , $AUC_{0-8 h}$, $AUC_{0-24 h}$ and $AUC_{0-\infty}$.

Results

Overall, 26 subjects were enrolled (arm A, $n = 14$; arm B, $n = 12$). One subject in each arm withdrew after randomization but before receiving the study agents. Thus, a total of 24 subjects were included in the final cohort. Baseline subject characteristics are summarized in Table 1. Grade 1 adverse events were reported during treatment by seven subjects, all of which resolved without specific therapy. One additional subject experienced a grade 2 adverse event (headache), which resolved with acetaminophen. During follow-up, one subject experienced a grade one adverse event (irregular

Table 2. Summary of pharmacokinetic variables, by sulindac moiety and formulation

	Sulfoxide		Sulfone		Sulfide	
	Capsule	Tablet	Capsule	Tablet	Capsule	Tablet
T_{max} (h)						
Mean (SD)	1.5 (1.3)	1.9 (1.2)	2.5 (1.4)	2.9 (1.0)	2.2 (1.5)	3.1 (1.6)
Range	0.5-6.0	0.5-6.0	1.5-8.0	1.5-6.0	1.5-8.0	1.5-8.0
C_{max} (μ g/mL)						
Mean (SD)	5.71 (2.17)	3.34 (1.64)	0.79 (0.31)	0.78 (0.50)	2.44 (0.81)	1.59 (0.48)
Range	0.86-8.63	0.96-7.35	0.24-1.50	0.30-2.84	1.02-4.47	0.63-2.43
$AUC_{0-8 h}$ (μ g/mL h)						
Mean (SD)	9.3 (2.7)	7.8 (2.7)*				
Range	3.9-14.9	3.6-12.1*				
$AUC_{0-24 h}$ (μ g/mL h)						
Mean (SD)			8.8 (3.6)	8.2 (3.6)	19.3 (7.0)	17.4 (6.1)*
Range			2.4-17.1	2.0-16.7	8.4-34.8	8.1-30.6*
AUC_{0-8} (μ g/mL h)						
Mean (SD)	10.6 (3.2)*	9.2 (4.0)	16.6 (10.8)	16.7 (10.5)*	26.8 (14.3)	26.9 (15.4)**
Range	5.8-18.1*	4.0-16.5	3.4-55.6	3.0-46.1*	8.7-76.3	5.0-66.5**

NOTE: Based on $n = 24$, except $n = 23$ (*) and $n = 22$ (**).

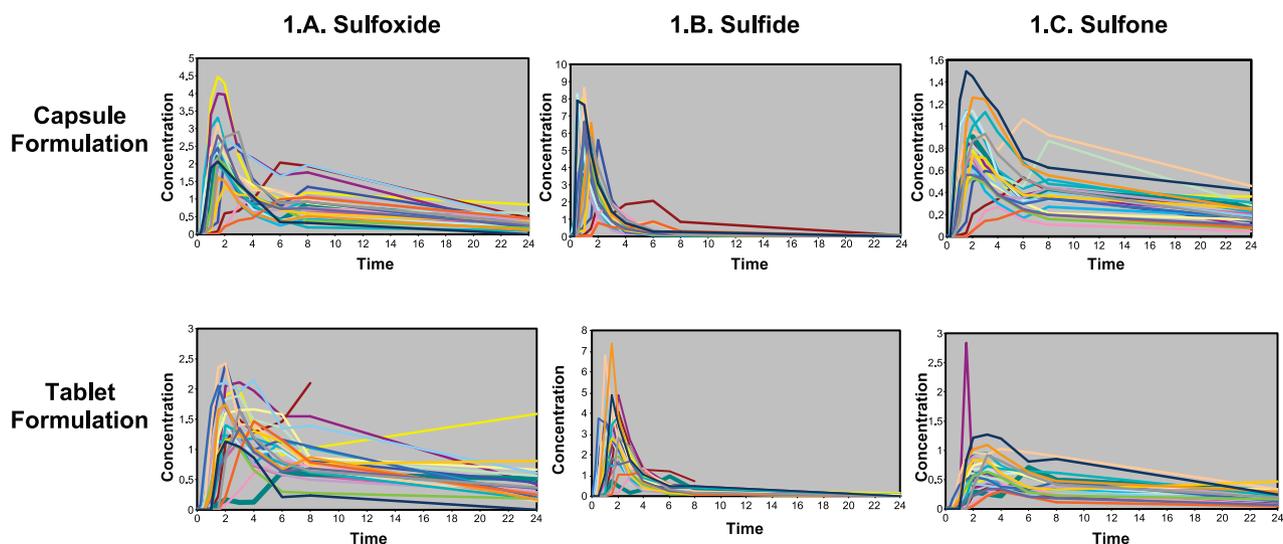


Figure 1. Concentration-Time Curves, by Sulindac Moiety.

menses). None of the observed adverse events were attributable to the study agents.

Mean (SD) and ranges for C_{max} , T_{max} , $AUC_{0-8 h}$, and $AUC_{0-24 h}$ for sulindac and each metabolite are provided in Table 2 for both formulations. Plasma concentration-time curves are illustrated in Fig. 1. Following a short delay of 0.46 h, a mean peak plasma concentration of 3.34 $\mu\text{g}/\text{mL}$ for sulindac sulfoxide was achieved 1.90 h after administration of the tablet formulation. The rate of absorption of the capsule formulation was found to be moderately faster, with a mean absorption delay of 0.30 h and a peak plasma concentration of 5.71 $\mu\text{g}/\text{mL}$ achieved at 1.52 h. The volume of distribution of sulindac sulfoxide following tablet or capsule administration was 93.2 ± 63.6 and 95.2 ± 75.1 L, respectively. Systemic exposure to the parent compound, as measured by $AUC_{0-8 h}$ and $AUC_{0-\infty}$, was ~25% greater for the capsule formulation compared with the tablet formulation. The results from the ANOVA models for the log-transformed measures of C_{max} , T_{max} , $AUC_{0-8 h}$, and $AUC_{0-\infty}$ revealed no statistically significant effects of intervention arm or period, suggesting absence of carryover or period effect ($P > 0.6$), but did reveal a statistically significant formulation effect ($P \leq 0.003$). The observed intersubject variability was much higher than expected, specifically 62% for C_{max} , 136% for T_{max} , 50% for $AUC_{0-\infty}$, and 45% for $AUC_{0-8 h}$. The 90% confidence intervals for each of the ratios of the average measures of sulindac sulfoxide systemic exposure did not lie within the 80.00% to 125.00% as shown in Table 3.

To further investigate the effect of this difference on exposure to the putative active species, we compared the bioavailability of sulindac sulfide and sulindac sulfone. Formation of the sulfide and sulfone metabolites was relatively rapid, with detectable concentrations occurring shortly after appearance of the parent compound (Table 2). Mean peak plasma concentrations of 1.59 $\mu\text{g}/\text{mL}$ for sulindac sulfide and 0.78 $\mu\text{g}/\text{mL}$ for exisulind were achieved 3.12 and 2.92 h, respectively, after administration of the tablet formulation. The capsule formulation yielded earlier peak plasma concen-

trations for both sulindac sulfide (2.19 h) and exisulind (2.50 h). C_{max} was also higher for sulindac sulfide (2.44 $\mu\text{g}/\text{mL}$), but not for exisulind (0.79 $\mu\text{g}/\text{mL}$), after capsule administration. As noted for the parent compound, ANOVA models for the log-transformed values of C_{max} , $AUC_{0-24 h}$, and $AUC_{0-\infty}$ found that both treatment arm and period were not statistically significant ($P > 0.3$), suggesting the absence of sequence or carryover effect. With the exception of the C_{max} ratio for sulindac sulfide (152%; 133-174%) and the $AUC_{0-24 h}$ ratio for exisulind (110%; 95-126%), the 90% confidence intervals for each of the ratios of the average measures of systemic exposure with respect to the sulfide and sulfone metabolites were within the 80.00% to 125.00% interval (Table 3).

Discussion

This study was done to compare the rate and extent of absorption for sulindac in capsule versus tablet formulations at the commonly prescribed dose of 150 mg. Inferences about the bioavailability of different drug formulations were made by comparing pharmacokinetic variables such as C_{max} , T_{max} , and AUC (23). Typically, bioavailability comparisons are based on plasma concentrations of the parent compound. However, for drugs that have a relatively short half-life, undetectable plasma

Table 3. Capsule-to-tablet ratio and associated 90% confidence interval estimates for the average measures of systemic exposure, by sulindac moiety

	Sulfoxide (%)	Sulfone (%)	Sulfide (%)
C_{max}	173 (143-210)	108 (94-123)	152 (133-174)
$AUC_{0-8 h}$	125 (114-136)	*	*
$AUC_{0-24 h}$	*	110 (95-126)	109 (99-119)
AUC_{0-8}	121 (110-132)	97 (83-114)	96 (82-111)

NOTE: See Table 2 for C_{max} and AUC units.

*Not evaluated.

levels, or known metabolites that affect efficacy and/or toxicity, assessments based on the parent compound alone may be misleading. Because sulindac metabolism yields two major metabolites with anticarcinogenic potential, we extended our comparisons of C_{max} , T_{max} , and AUC to include sulindac sulfide and exisulind. These additional data provided stronger support for sulindac capsules being used as a therapeutic alternative for sulindac tablets and underscore the importance of considering all metabolites in an equivalence determination for highly transformed drugs.

In the present single-dose, two-period crossover trial, sulindac bioavailability appeared to be higher for the capsule compared with the tablet formulation based on test-to-reference pharmacokinetic ratios for sulindac sulfoxide. Reassuringly, the pharmacokinetic variables observed for sulindac in the present trial are similar to those reported in earlier studies (19, 24, 25). Of note, Kanfer et al. reported on the bioavailability of a liquid and tablet formulation and found that sulindac peak concentrations were earlier and the AUC was higher for the liquid formulation compared to the tablet formulation (19). Greater bioavailability of the liquid formulation was attributed to the formation of particulate dispersion in gastric juices that was readily absorbed after administration of the oral liquid. In contrast, sulindac absorption from tablets may be impeded by agglomeration when tablets undergo disintegration before dispersion of the particulate drug. Our observations of higher sulindac bioavailability with the capsule formulation are consistent with the observations for the liquid formulation, because dissolution of the gelatin capsule produces a particulate dispersion, similar to the liquid formulation.

To further investigate the effect of this difference on exposure to the putative active species, we compared the bioavailability of sulindac sulfide and sulindac sulfone in secondary *post hoc* analyses. Independent comparisons analyses for each of the metabolites provided at least modest support for comparable bioavailability between the test and reference formulations. As with the parent drug, the peak concentration of sulindac sulfide was substantially higher after administration of the capsule formulation. However, the rate and extent of sulindac sulfide formation was comparable based on a comparison of T_{max} and AUC values but not C_{max} values. As noted for the parent compound, the higher C_{max} value achieved following administration of the capsule is consistent with release of a particulate dispersion following dissolution of the gelatin capsule. The rate and extent of exisulind formation was similar based on the measurement of C_{max} , T_{max} , and AUC values. Because the most commonly observed adverse events associated with sulindac appear to be dose related rather than peak concentration related, we believe that the capsule formulation may be substituted for the tablet formulation in future clinical trials if appropriate toxicity monitoring is employed.

There does not appear to be a clear consensus on the methods to be used for evaluating bioequivalence when metabolites play a role in the pharmacologic effect, especially when the parent compound does not undergo first-pass metabolism (25, 26). A recent commentary on bioequivalence studies concluded that bioequivalence should be based on the parent drug when the parent drug concentration-time profile can be adequately

characterized but suggested that metabolite concentration data may be used when an inactive prodrug is converted to active metabolites (27). Whereas exposure to sulindac sulfoxide from the two formulations under investigation in our study was not equivalent, both formulations yielded similar exposure to the sulfone and sulfide metabolites.

Further analyses of these data using other approaches may provide additional insights regarding the bioavailability of capsule or tablet formulations in future sulindac chemoprevention trials. First, the data may be analyzed by compartmental analysis using either standard nonlinear least squares regression or Bayesian approaches to estimate AUC. Second, comparable bioavailability testing may be done on the sum of the parent compound and each metabolite, although some suggest that this latter approach may be misleading (28). Lastly, repeat assessment using either a replicate study design or group-sequential study design could be considered given the relatively small sample size of our two-period crossover trial.

In summary, sulindac remains a promising candidate chemoprevention agent with potentially beneficial effects in multiple target organs. The currently reported results complement and extend limited existing data on the pharmacokinetics of sulindac sulfoxide as well as its two major metabolites. Sulindac capsule and tablet formulations appear to provide similar chemopreventive exposure based on the pharmacokinetic analysis of the sulindac sulfide and sulindac sulfone metabolites. Continued evaluation of the chemopreventive potential of sulindac requires additional investigation in well-designed randomized, placebo-controlled trials. Data from our study support the application of sulindac capsules, for which matching placebo supplies can be readily manufactured, in future blinded chemoprevention trials to expedite further agent development.

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