Comparison of Zafirlukast (Accolate®) Absorption After Oral and Colonic Administration in Humans

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Purpose. This study characterized the gastrointestinal (GI) absorption of zafirlukast after oral and colonic administration in humans.

Methods. Five healthy subjects received zafirlukast solution (40 mg) orally and via an oroenteric tube into the colon in a randomized, crossover fashion. Two additional subjects were dosed into the distal ileum. Serial blood samples were obtained and plasma concentrations were quantitated by HPLC.

Results. Mean ± SD pharmacokinetic parameters after oral vs. colonic administration were: AUC_∞ of 2076 ± 548 vs. 602 ± 373 ng*h/mL, respectively, and C_{max} of 697 ± 314 vs. 194 ± 316 ng/mL, respectively. Mean colon:oral AUC_∞ and C_{max} were 0.29 and 0.30, respectively. Median t_{max} values were 2.0 and 1.35 hr after oral and colonic administration. First-order absorption rate constants (K_a and K_{ac}) were estimated from a two-compartment model with first-order elimination. K_{ac}:K_a was <0.5 in 4 of the 5 subjects dosed in the colon.

Conclusions. Zafirlukast was absorbed at multiple sites in the GI tract. The rate and extent of zafirlukast absorption was less after colonic than oral administration. Zafirlukast was significantly absorbed in the distal ileum. This study demonstrated that gamma scintigraphy, digital radiography, and fluoroscopy can be used to track the movement and confirm the location of the oroenteric tube in the GI tract.

KEY WORDS: zafirlukast; Accolate®; absorption; colon; and oroenteric.

INTRODUCTION

Asthma is a chronic inflammatory disorder affecting more than 100 million people worldwide. The incidence and cost associated with severe asthma is increasing (1). Emphasis on the treatment of severe asthma has focused on agents that modulate the inflammation process, such as corticosteroids, cromolyn, and leukotriene receptor antagonists. Leukotrienes are synthesized via the 5-lipooxygenase pathway and exhibit bronchoconstrictive properties by increasing mucus production, cellular infiltration of airways, airway hyperactivity, vascular permeability causing edema of endothelial cells, and a decrease in mucocillary transport (1,2). The bronchoconstrictive properties of leukotrienes are approximately 1000 times more potent than histamines (1,2).

Zafirlukast (Accolate®) is a leukotriene receptor antagonist indicated in the treatment of chronic asthma that has shown clinical efficacy in challenge models of asthma by blocking early and late-phase response to allergen challenge and attenuation of exercise and cold air induced bronchoconstriction (3). In longer term clinical trials, zafirlukast has demonstrated sustained improvements in asthma symptoms and airway function. Currently, zafirlukast has FDA approval for the prophylaxis and chronic treatment of asthma in patients ≥7 years. Clinical studies have demonstrated that zafirlukast plasma concentrations are inversely correlated with a reduction in airway conduction caused by leukotrienes (2).

The pharmacokinetic disposition of zafirlukast in humans has been described in part. A two-compartment model best describes the pharmacokinetic disposition of zafirlukast. Males administered a single oral dose of 0.4 mg/kg demonstrated a C_{max} of 292 ng/mL, t_{max} of 1.5 hours, and AUC of 1080 ng/hr mL, with a $t_{1/2}$ of approximately 7.1 hours (4). The absolute bioavailability of zafirlukast has not been reported because a formulation suitable for intravenous administration in humans has not been developed. However, the absolute bioavailability based on an intravenous solution in rats and dogs ranged from 60–70%. Also, the bioavailability of the commercial tablet is approximately 100% relative to the oral solution used in this study, based on AUC (4) (though the commercial tablet was not specifically evaluated in this trial). Zafirlukast is thought to be rapidly and extensively metabolized by the liver; biliary secretion is the major route of elimination. In bile-duct-cannulated rats and dogs administered radiolabeled zafirlukast, 79–88% of the dose was recovered in the bile (less than 4% of the dose was recovered in the urine and feces) (5).

Zafirlukast currently is approved for twice daily administration. A modified release dosage form administered once daily may be more convenient for patients while helping them achieve consistent control of their asthma throughout the day. Knowledge of the absorption characteristics of zafirlukast at different sites in the gastrointestinal tract will facilitate development of a modified release dosage form. The primary objective of this study was to characterize and compare the absorption of zafirlukast after oral and colonic administration. A secondary objective was to evaluate the utility of gamma scintigraphy, digital radiography, and fluoroscopy procedures to verify the movement and confirm the location of the oroenteric tube at different sites in the GI tract.

MATERIALS AND METHODS

This was a randomized, open-label, two-period crossover study in 8 healthy male volunteers (Table I). Zafirlukast (Accolate® AstraZeneca, Wilmington, DE; 40mg/80mL in 20% polyethylene glycol) was administered orally and via an oroenteric

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Table 1. Subject Demographics

Subject number	Age (years)	Weight (kg)	Height (cm)	% From IBW	Ethnicity	Oroenteric dosing location
101	19	87.1	190.7	2.9	Asian/Native American	Not done*
102	23	82.7	188.0	0.6	Caucasian	Colon
103	29	78.5	171.4	16.8	Asian	Colon
104	20	65.9	174.0	17.2	Caucasian	Distal ileum
105	29	73.9	177.0	2.2	Caucasian	Colon
106	30	81.5	182.8	5.1	Black	Colon
107	26	73.1	174.3	4.7	Caucasian	Colon
108	28	92.7	179.5	24.4	Caucasian	Distal ileum
Mean	25.5	79.4	179.7	9.2		
SD	4.0	7.9	6.5	8.3		
Range	(19–30)	(65.9–92.7)	(171.4–190.7)	(0.6–24.4)		

* Subject dropped out of study after completing oral administration period for personal reasons; data were excluded from analysis.

tube into the colon, with a minimum of a 3-day washout between the 2 periods. This study was approved by the Committee for the Protection of the Rights of Human Subjects of the University of North Carolina School of Medicine, and conducted in the General Clinical Research Center (GCRC) at the University of North Carolina Hospitals and Clinics.

All subjects gave written informed consent prior to screening procedures. Physical examination, including vital sign measurements (blood pressure and heart rate), ECG, and laboratory tests revealed no clinically significant abnormalities. Subjects were nonsmokers and received no antibiotics for 2 months prior to the study, and abstained from all medications, alcohol, and caffeine for 72 hours prior to and for 36 hours after zafirlukast administration. To decrease the variability of zafirlukast absorption due to the effects of food, all subjects received low fat/no caffeine meals and snacks. The times of meals and snacks along with the caloric content, including protein, carbohydrate, and fat did not differ between the two treatment periods.

Subjects were randomized into one of two treatment sequences and admitted to the GCRC for their first treatment within 2 weeks after screening.

Oral Administration

Subjects were admitted to the GCRC on day 1, the evening prior to administration of zafirlukast. They were assessed for compliance with protocol requirements and received a meal and snack at 1800 and 2200, respectively.

On day 2, venous access for blood sampling was obtained by having a catheter placed in a forearm vein and kept patent by a normal saline infusion. In order to minimize variability in the amount of zafirlukast administered in different treatment periods due to potential binding of zafirlukast to the oroenteric tube, the orally administered zafirlukast solution first was flushed through 3.3 meters of oroenteric tubing identical to the tubing used for administration into the colon. Subsequently, the tube was flushed with 10 mL of distilled water and the entire volume was collected. This zafirlukast dosing solution was administered orally at approximately 0800. The subject remained in a semi-reclining position, and nothing was administered by mouth, including water, for 4 hours after administration of zafirlukast. The subject received lunch 4 hours after zafirlukast administration at approximately 1200.

Blood samples (7 mL) for both the oral and colon administration periods were obtained pre-dose and at scheduled times after administration: 15, 30, 45, 60, 75, 90 minutes, and 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, and 36 hours. Samples were centrifuged at 2000 RPM for 15 minutes, and the plasma was stored at −20°C until analysis. Samples were analyzed within 4 months of collection.

Oroenteric Administration

Subjects were admitted to the GCRC on day 1, the day prior to administration of zafirlukast, and were assessed for compliance with protocol requirements. At approximately 1300, the subject swallowed the oroenteric tube. The triple-lumen polyvinyl chloride oroenteric tube was flexible, clear, approximately 3.3 meters in length, and consisted of a single and a double lumen tube fastened side-by-side using tetrahydrofuran as an adhesive. The single lumen tube, which was used for drug delivery, had an internal diameter (ID) of 1.14 mm. Each lumen of the double lumen tube had an ID of 0.8 mm. The overall outer diameter of the three lumen oroenteric tube was approximately 3.6 mm. Both lumens of the double lumen tube opened into a balloon. The balloon consisted of the distal halves of two condoms, one inside the other, secured to the end of the double-lumen tube by suture ligatures to form an air-tight seal (tested under water with the balloon inflated). One lumen was designated for instillation and withdrawal of air from the balloon. The other lumen was filled with radiolabeled technetium during the study which allowed the position of the tube to be tracked by gamma scintigraphy.

After approximately 50 cm of tube was swallowed, a small amount of technetium (250 μCi/mL; approximately 0.3–0.6 mL) was injected into the designated lumen of the triple lumen oroenteric tube and the subject's abdomen was viewed by gamma scintigraphy (Fig. 1). Once it was confirmed that the tube was in the jejunum, the technetium was withdrawn and discarded, and the balloon was inflated with 10–15mL of air. The propulsive effects of intestinal peristalsis on the inflated balloon were utilized to facilitate movement of the tube through the gastrointestinal tract as described previously (6,7). Gastografin was added to the lumen of the tube formerly containing technetium and the location of the tube in the small intestine was determined at intervals with digital still radiographs or

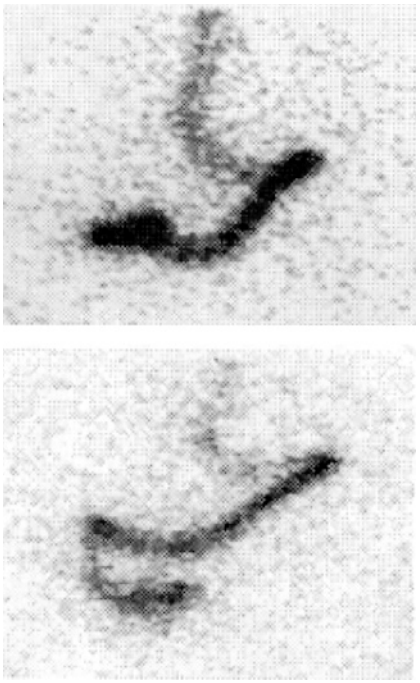

Fig. 1. Gamma camera image of the oroenteric tube filled with a trace amount of technicium prior to (top) and after (bottom) movement of the tube from the stomach through the pyloric valve into the small intestine.

up to 1 minute of fluoroscopy using filters. These techniques dramatically limited radiation exposure. Once the tip of the tube was in the cecum or distal ileum, the balloon was deflated, any loops of tube in the stomach were removed, and the tube was taped to the subject's cheek to retard further advancement. The subject received a snack and meal at 1800 and 2200, respectively.

On day 2, venous access for blood sampling was obtained by a catheter placed in a forearm vein which was kept patent by a normal saline infusion. At 0700, the position of the tip of the tube in the colon was confirmed radiographically, as described, after injection of 50 ml of air through the drug delivery port to provide contrast in the bowel lumen. If the tube had not reached the colon at this time, the balloon was inflated and the tube was allowed to migrate further down the GI tract to the desired location. If the tube had migrated past the cecum, the tube was pulled back gently, and the position of the tube was monitored by fluoroscopy until the desired location was reached for dosing. Once the tube position was confirmed, zafirlukast solution was administered via the oroenteric tube followed by 10 mL of distilled water. The subject remained in a semi-reclining position, and nothing was administered by mouth, including water, for 4 hours after administration of zafirlukast. Blood samples were collected as described previously. The tube was removed 4 hours after dosing by slow, gentle pulling with a 5 minute stop when 50–60 cm of tube remained in order to allow gastric acid to wash cecal contents from the surface of the balloon and tube. The subject received meals and snacks at 1200, 1800, and 2200, respectively.

On day 3 for both treatment periods, after the 24-hour blood sample was drawn, the venous access was removed and the subject was released from the GCRC. The subject returned to the GCRC at 36 hours post-dose for the final blood sample and exit evaluation, including a physical examination, vital signs, and clinical laboratory tests.

Radiologic Procedures

Heavily filtered x-ray beam fluoroscopy and radiography procedures developed at the University of North Carolina Radiology Department, were conducted using Fuji computed radiography imaging plates with a relative system speed of 4000. A high kVp (120) beam with a stack filter composed of 0.1 mm molybdenum, 0.5 mm copper, and 2 mm aluminum was used. The estimated systemic exposure (ESE) for a 24 cm abdomen filtered x-ray was 25–30 mR. Using the same stack filter, fluoroscopic ESE for a 24 cm abdomen was approximately 900 mR/min at 120 kVp. The fluoroscopic images were acquired using very short (<5 seconds) exposure times and displayed with the last image hold feature of the video system.

Assay Procedure

Zafirlukast concentrations in plasma were determined by HPLC with fluorescence detection (8). The lower and upper limits of quantitation were 0.750 ng/mL and 150 ng/mL, respectively. Overall precision was 2.8% over the range of validated concentrations.

Pharmacokinetic Analysis

Plasma zafirlukast concentration versus time data for each subject were analyzed by noncompartmental methods. The peak concentration (C_{max}) and time to peak concentration (t_{max}) of zafirlukast in plasma were determined from visual inspection of the observed data. Plasma zafirlukast concentrations that were judged to be in the terminal phase were used to obtain the terminal elimination rate constant (λ_z) by log-linear regression. The area under the concentration-time curve (AUC_t), truncated at the last observed concentration (C_t), was calculated by applying the linear trapezoidal rule to C_{max} and the log-linear trapezoidal rule thereafter. The total AUC_∞ was estimated as follows: $AUC_\infty = (AUC_t) + C_t/\lambda_z$. The percentage of AUC_∞ obtained by extrapolation ($AUC_{\%ext}$) was estimated as follows: $AUC_{\%ext} = ((AUC_\infty - AUC_t)/ AUC_\infty) \cdot 100$. The terminal elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda$

A two-compartmental pharmacokinetic model with first-order elimination was fit simultaneously to the observed zafirlukast concentration-time profiles after oral and colonic administration in each subject. The first-order rate constants, K_a and K_{ac}, were used to describe zafirlukast absorption after oral and colonic administration, respectively. Complete zafirlukast absorption was assumed after oral administration. The fraction of the zafirlukast dose absorbed after colonic administration was determined by the ratio of the AUC_∞ values calculated after oral and colonic administration. Modeling was performed using WinNonlin Version 1.5.

Statistical Analysis

A two-period crossover analysis of variance (ANOVA) was used to determine any statistically significant differences in the pharmacokinetic parameters, AUC_∞ and C_{max}, for zafirlukast

between oral and colonic administration. All statistical comparisons of the individual pharmacokinetic parameters were performed on log transformed zafirlukast data. Differences were considered statistically significant when the p-value was less than 0.05.

RESULTS

All zafirlukast administrations were well tolerated by the subjects and no significant drug related adverse events, including significant physical or laboratory changes were noted. Due to the difficulty in positioning the oroenteric tube into the colon, subjects #104 and #108 were administered zafirlukast proximal to the colon in the distal ileum. Subsequently, data from these subjects were excluded from the primary analysis.

Noncompartmental Analysis

Individual and mean plasma zafirlukast concentration-time profiles after oral and colonic administration are shown in Fig. 2. Individual and mean plasma zafirlukast C_{max} and AUC_∞ values after oral and colonic administration are presented in Fig. 3. Less than 5% of the total AUC_∞ value was extrapolated in all cases after oral administration, and less than 11% was extrapolated after colonic administration. Plasma zafirlukast AUC_∞ values were significantly decreased ($p = 0.04$) after colonic compared to oral administration, as represented by a mean ± SD colon:oral AUC_∞ ratio of 0.29 ± 0.19. Similarly, plasma zafirlukast C_{max} values were significantly decreased ($p = 0.01$) after colonic compared to oral administration, as represented by a mean ± SD colon:oral C_{max} ratio of 0.30 ± 0.52. The terminal elimination rate constant was not statistically different ($p = 0.32$). The half-life values after oral administration ranged from 11.7–20.2 hr in four subjects, with one outlier at 43.7 hr. The half-life values after colonic administration ranged from 8.2–15.0 hr in four subjects, with one outlier (same subject as above) at 20.7 hr. Mean pharmacokinetic parameters are presented in Table II.

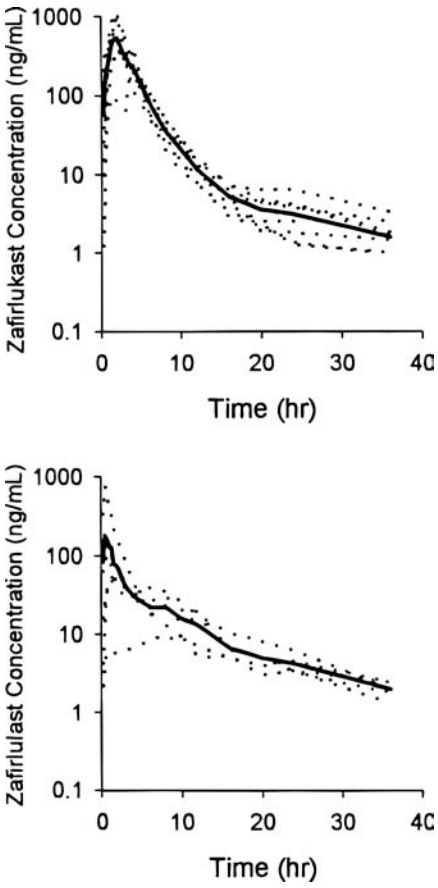

Fig. 2. Individual (dotted curves) and mean (solid curve) plasma zafirlukast concentration-time profiles after oral (top) and colonic (bottom) administration.

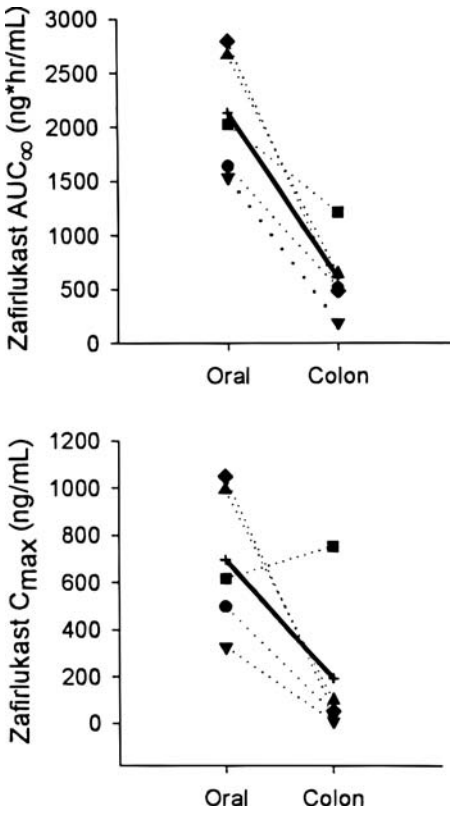

Fig. 3. Individual (●, subject 102; ■, subject 103; ▲, subject 105; ▼, subject 106; ♦, subject 107) and mean (+---+) zafirlukast AUC_∞ (top) and C_{max} (bottom) values after oral and colonic administration.

Table II. Pharmacokinetic Parameters[a]

Treatment	AUC_∞ (ng*hr/mL)	$AUC_{\%ext}$ (%)	$AUC_{0\text{-}t}$ (ng*hr/mL)	C_{max} (ng/mL)	t_{max} (hr)
Oral[b]	2076	2.9	2015	697	2.0
	[548]	[1.2]	[529]	[314]	[1.1–3.0]
Colon[b]	602*	7.6	561*	194*	1.3
	[373]	[3.4]	[355]	[316]	[0.5–10]
Oral[c]	1978	1.6	1947	610	1.5
Distal ileum[c]	2481	1.5	2447	1735	0.6

[a] AUC_∞, $AUC_{\%ext}$, $AUC_{0\text{-}t}$, and C_{max} values represent arithmetic mean [SD]; t_{max} values represent median [range].
[b] n = 5.
[c] Arithmetic mean values; n = 2.
* $p < 0.05$ (comparison of oral and colonic administration).

Table III. Estimated Absorption Rate Constants (K_a and K_{ac}) After Oral and Colonic Administration

	Oral		Colon		Ratio
Subject	K_a	CV%	K_{ac}	CV%	K_{ac}/K_a
102	0.74	30.3	0.14	18.3	0.19
103	0.73	14.6	3.63	30.0	4.97
105	0.58	105.1	0.28	85.8	0.48
106	0.46	112.0	0.08	68.6	0.17
107	0.52	157.0	0.19	114.5	0.37

No formal statistical analyses were conducted on pharmacokinetic parameters for subjects dosed in the distal ileum due to the small sample size (n = 2). However, AUC_∞ and C_{max} values after distal ileal administration of zafirlukast (Table II) were similar to or greater than those values observed after oral administration.

Compartmental Analysis

The ratio of first-order absorption rate constants for zafirlukast after colonic (K_{ac}) and oral (K_a) administration was <0.5 in 4 of the 5 subjects dosed in the colon (Table III). Representative observed and predicted zafirlukast plasma concentration-time profiles for subject 102 are plotted in Fig. 4.

DISCUSSION

Frequently there are significant differences for many drugs in AUC and Cmax values after oral versus colonic administration. Mean AUC_∞ and C_{max} values for zafirlukast were statistically different after oral and colonic administration, indicating that the rate and extent of zafirlukast absorption from the colon were less than that observed after oral administration. AUC_∞ and C_{max} ratios demonstrated that the exposure of zafirlukast after colonic administration was approximately 30% of that observed after oral administration. Furthermore, comparison of the first-order absorption rate constants suggested that the rate of zafirlukast absorption was much less from the colon than after oral administration in 4 out of 5 subjects.

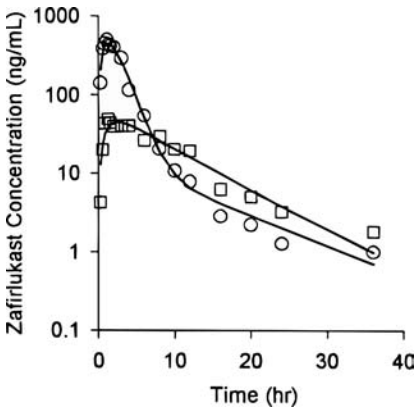

Fig. 4. Representative observed (symbols) and predicted (solid curves) zafirlukast plasma concentration-time profiles after oral (○) and colonic (□) administration for subject 102.

The extent of absorption of drugs from the colon exhibits a wide range and appears to be compound specific. Ondansetron is well absorbed in the colon, with an absolute bioavailability of 74% after colonic administration (9). Benazepril hydrochloride also demonstrates an appreciable amount of colonic absorption with 23% of the drug reaching the systemic circulation when administered via the colon compared to oral administration (10). Ranitidine has a lower extent of colonic absorption with a relative bioavailability of 15% when compared to ranitidine administered into the stomach or jejunum (7). Amoxicillin is not absorbed in the colon when administered in all colonic regions (11). Thus the extent of colonic absorption of zafirlukast compares favorably with other drugs administered into the colon.

No formal statistical analysis was conducted with the pharmacokinetic data from subjects dosed in the terminal ileum. However, AUC_∞ and C_{max} values after administration into the distal ileum were similar to or greater than those values observed after oral administration. In contrast, zafirlukast absorption from the colon is low relative to absorption from the small intestine. These results imply that zafirlukast is absorbed throughout the GI tract, with the majority of orally administered zafirlukast absorbed in the small intestine.

In clinical studies, oroenteric tube placement often is difficult, and these procedures only approximate drug delivery to a specific region of the gastrointestinal tract. This study demonstrated that gamma scintigraphy could be used to confirm that the oroenteric tube, containing radiolabeled technetium, had passed through the pyloric valve into the small intestine. In other studies, pH probes incorporated in the tube have been used for this purpose (7). Filtered digital radiography and fluoroscopy were used to confirm the movement and location of the tube in the GI tract. Other techniques to position the oroenteric tube include the use of pH probes and radiotelemetry with a Heidelberg capsule (7,12–14). However, these methods can be technically more challenging with *in vitro* calibration and activation prior to use. Furthermore, the addition of probes or capsules may increase the outer diameter or bulkiness of the oroenteric tubes, thus increasing discomfort when subjects swallow the tube and when the tube is removed.

In conclusion, results of this study indicate that zafirlukast was absorbed throughout the small intestine, and to a lesser extent in the colon. Compared to oral administration, the rate and extent of colonic absorption was approximately 30%. In addition, gamma scintigraphy, digital radiography, and fluoroscopy procedures were utilized successfully to determine the movement and location of the oroenteric tube within the GI tract.

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