Sumatriptan Absorption from Different Regions of the Human Gastrointestinal Tract

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Received February 11, 1994; accepted August 24, 1994

Sumatriptan exhibits low oral bioavailability partly due to presystemic metabolism, which may vary with regional differences in metabolic activity throughout the gastrointestinal tract. This study evaluated sumatriptan absorption in humans after administration orally and by oroenteric tube into the jejunum and cecum. Because the site of cecal administration varied, pharmacokinetic parameters for sumatriptan and its major metabolite were compared statistically only after oral and jejunal administration. One-half of the oral dose was recovered in the urine as parent (3%) and metabolite (46%). Sumatriptan was absorbed throughout the gastrointestinal tract; absorption was similar after oral and jejunal administration, and less after cecal administration. The metabolite AUC and the AUC ratio (metabolite/parent) were significantly lower after jejunal compared to oral administration; the AUC ratio was two-fold lower after cecal administration. Results suggest that presystemic metabolism of sumatriptan varies throughout the gastrointestinal tract and/or regional differences exist in the absorption of metabolite formed within the gastrointestinal tract.

KEY WORDS: sumatriptan; gastrointestinal tract; absorption; metabolism; pharmacokinetics.

INTRODUCTION

Sumatriptan (GR43175) is a selective 5-HT_1 receptor agonist [1] effective for the treatment of migraine. The mechanism of action is not precisely known, although the therapeutic effect is believed to be due to a selective vasoconstriction of the carotid arterial circulation via activation of 5-HT_1 receptors.

Sumatriptan is absorbed rapidly after oral administration and has an elimination half-life of approximately 2 hours [2]. The extent of sumatriptan absorption is dose-independent over the dosage range studied (up to 400 mg) [3]. Multiple peaks can occur in the plasma sumatriptan concentration-time profile after oral dosing, resulting in a variable time to maximum concentration (T_{max} = 0.5 − 6.0 hours) [2,3]. This phenomenon has been observed with a number of drugs, such as H_2-receptor antagonists [4,5,6]. Sumatriptan bioavailability and kinetic parameters are not significantly different in the fed and fasted states [2].

The low bioavailability (approximately 14%) and low fecal recovery (approximately 9% as parent and 11% as metabolite), coupled with the high non-renal clearance (approximately 80%) after oral administration suggest that sumatriptan is eliminated predominantly by metabolism [2]. The major metabolite of sumatriptan in humans is the indole acetic acid analog (GR49336), which has no known pharmacologic activity. [2]. A portion of this metabolite is subsequently glucuronidated on the carboxylic acid moiety. Monoamine oxidase (MAO-A) is the major enzyme responsible for the metabolism of sumatriptan in human liver [7]. After oral administration of ^{14}C-sumatriptan to humans, 57% of the dose was excreted in the urine and 38% in the feces. It is unknown whether metabolite recovered in the feces is derived from gastrointestinal metabolism or biliary excretion. Urinary recovery of sumatriptan, the indole acetic acid metabolite, and the glucuronide conjugate accounted for 3%, 35%, and 8% respectively, of the dose [2]. Plasma concentrations of the major metabolite after oral administration are 6-7 times higher than those of the parent. The metabolite displays a half-life similar to the parent, indicating that the clearance may be formation-rate limited [2].

Monoamine oxidase enzymes are distributed widely throughout the body including the gastrointestinal tract [8]. Enzymes within the gut and/or gut wall in the small intestine may metabolize sumatriptan, and may be responsible in part for the first-pass effect. Since metabolic activity varies in different regions of the gastrointestinal tract [8], the first-pass effect of sumatriptan may be influenced by the site of drug administration. The objective of this study was to determine and compare the absorption profile of sumatriptan when delivered to various anatomical regions of the human gastrointestinal tract.

MATERIALS AND METHODS

This was an open-label study comparing the absorption characteristics of sumatriptan. Sumatriptan for subcutaneous injection (Imitrex® Glaxo Inc., Research Triangle Park, NC; 6 mg/0.5 mL in sodium chloride) was administered orally for the first dose and via an oroenteric tube to the jejunum and cecum for the second and third doses, respectively, with a 24 hr washout period between each dose.

This study was performed in 8 healthy male volunteers between the ages of 23 and 35 years (mean = 27 years), having body weights of 140-190 pounds (mean = 168 pounds), heights of 68-77 inches (mean = 72 inches) and within 15 % of their ideal body weight. The study protocol and process for obtaining informed consent were approved by the Committee for the Protection of the Rights of Human Subjects of the University of North Carolina School of Medicine. All subjects gave written consent prior to screening. Physical examination and vital sign measurements (blood

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This work was presented in part at the 8th Annual Meeting of the American Association of Pharmaceutical Scientists, November 14–18, 1993, Lake Buena Vista, Florida.

0724-8741/95/0100-0138$07.50/0

pressure, pulse rate), ECG, and laboratory tests revealed no clinically significant abnormalities.

Subjects received two low fat/no caffeine meals (lunch, approximately 4 hours after dosing, and dinner) with the same caloric content and nutrients, and a low fat/no caffeine snack (10:00 p.m.) daily. Water was allowed *ad libitum* throughout the study. Although food has no significant effect on the oral bioavailability of sumatriptan [2], subjects fasted for at least 8 hours prior to drug administration to reduce variability in gastric emptying and intestinal motility.

Clinical Procedures. Subjects were admitted to the General Clinical Research Center of the University of North Carolina Hospitals on Day 1, the evening prior to drug administration. They were queried to assure that they had been compliant with the protocol requirements. Subjects received dinner and a snack at the respective meal times.

On Day 2, a venous access for blood sampling was placed in a forearm vein and kept patent by a normal saline infusion. At approximately 8:00 A.M., a 50 mg oral dose of sumatriptan was administered followed by 100 mL of water. Subjects remained in a semi-reclining position until four hours post dosing. Blood samples (7 mL) were obtained predose and at scheduled times after drug administration: 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hr. The samples were centrifuged and serum was divided into two separate aliquots for determination of sumatriptan and metabolite concentrations. Urine was collected and pooled during the following intervals: 0-4, 4-8, and 8-12 hours. The urine volume was recorded and two separate 10 mL aliquots (for determination of sumatriptan and metabolite concentrations) were collected. All samples were stored at − 20°C and analyzed within four months of collection.

Four hours after drug administration, an oroenteric tube was inserted. The oroenteric tube utilized was a flexible, 4.5-meter long, three lumen tube of approximately 5 mm diameter with a tungsten weighted tip. One lumen of this tube was fitted with two pH probes, one at the level of the drug delivery port near the tip and one 35 cm proximal. Determination of pH by these probes facilitated placement of the end of the tube into the jejunum and minimized the need for x-rays to confirm placement. The second lumen was used for drug administration; its port was located at the distal pH probe. Air (10-15 mL) was instilled into the third lumen, when necessary, to inflate the balloon surrounding the weight. The propulsive effects of intestinal peristalsis on the inflated balloon were utilized to facilitate movement of the tube through the gastrointestinal tract. This technique is described in the literature [9,10]. The tube was allowed to advance past the ligament of Treitz, and was taped at the subject's mouth to prevent further advancement. Positioning of the tip of the tube was achieved when both pH probes recorded alkaline values.

One hour prior to the scheduled dose on Day 3, the tube was slowly withdrawn until the proximal probe showed a sudden drop in pH indicating that it was very near the pylorus, and that the distal probe and drug delivery port were in the jejunum, 35cm distal to the pylorus. The position of the tube was confirmed with a plain abdominal radiograph. Once placement was confirmed, 50 mg of sumatriptan was administered via the oroenteric tube. Subjects swallowed 90 mL of water after sumatriptan administration and the tube was flushed with 10 mL of normal saline. Blood and urine were collected as described on Day 2. Four hours after the dose was administered, the balloon was inflated with 10-15 mL of air, and the tube was allowed to advance.

Five hours after tube advancement commenced, the position of the tube was determined via another plain abdominal radiograph using high speed film and special filters to minimize radiation exposure. If the tube was not in the cecum, the distance from the cecum was estimated and the tube was allowed to continue to advance. If the tube was in the cecum, the balloon was deflated and the tube was taped to the subject's face to prevent further advancement.

One hour prior to the scheduled dose on Day 4, the position of the tube was confirmed again by radiograph. When the tube was judged to be in the cecum and the balloon deflated, sumatriptan was administered as described on Day 3, and blood and urine samples were collected as described previously. The tube was removed four hours after dosing by slow, gentle pulling through the mouth.

Exit evaluations were carried out 12 hours after the final administration of sumatriptan for all subjects. Each subject underwent a physical examination, vital sign determinations, and clinical laboratory tests. In addition, each subject was questioned again regarding possible adverse events. Subjects were discharged if physical examination findings and vital signs were normal, and no study-drug-related complaints were elicited.

Assay Procedure. Sumatriptan concentrations in serum and urine were determined by HPLC with electrochemical and fluorescence detection, respectively [11]. For the analysis of serum sumatriptan, 100 μL 4 M sodium hydroxide was added to 1 mL human serum, extracted into 2.6 mL 4:1 (v/v) ethyl acetate:methylene chloride, and back-extracted into 250 μL 0.05 M potassium phosphate buffer (pH 7). Samples were injected onto a C18 reverse phase HPLC column (125 × 4.6 mm; 5 μm particle size) fitted with a guard column; an ESA Coulochem model 5100A coulometric detector (+0.8 V) was employed. The mobile phase was 40% 0.05M phosphate buffer (pH 7) in methanol flowing at a rate of 1 mL/min. Urine sumatriptan concentrations were determined by injecting 20 μL human urine directly onto a C18 reverse phase HPLC column connected to a fluorescence detector (excitation and emission wavelengths were 280 and 350 nm, respectively).

Metabolite (GR49336) concentrations in serum and urine were determined by HPLC with electrochemical and ultraviolet absorbance detection, respectively. For the analysis of serum metabolite, 200 μL human serum was precipitated with 150 μL 5% sulfosalicylic acid and centrifuged for 15 minutes at 4000 rpm. A 130 μL aliquot of supernatant was transferred to an autosampler vial and 25 μL of the solution was injected on the C18 reverse phase HPLC column (100 × 4.6 mm; 3 μm particle size) fitted with a guard column. Coulometric detection was conducted with a glassy carbon electrode at +825 mV. The mobile phase was 13.5% methanol in 0.05 M citric acid buffer (pH 4.25) for 0-18 minutes isocratic, followed by 70% methanol in citric acid buffer from 18-24 minutes to remove residual material from the column. For the analysis of urine metabolite, 250 μL human urine was diluted with 750 uL 12% methanol in 0.05 M ammonium acetate (pH 4.5). A 100 μL aliquot was transferred to an autosampler vial and 25 μL of solution was injected on the C18 reverse phase HPLC column (100 × 4.6 mm; 3 μm

particle size) fitted with a guard column; an ultraviolet absorbance detector at 220 nm was employed.

Serum sumatriptan and metabolite standard curves were linear over the concentration range of 0.5 to 60 ng/mL and 10 to 500 ng/mL, respectively. The within- and between-day coefficients of variation (%CV) for sumatriptan were 2.6 and 9.1%, respectively; within- and between-day %CV were 8.7 and 16.5%, respectively, for metabolite. Urine sumatriptan and metabolite concentrations were linear over the range of 0.25 to 10 μg/mL and 0.25 to 20 μg/mL, respectively. The within- and between-day %CV for sumatriptan were 2.2 and 10.6%, respectively; within- and between-day %CV were 1.1 and 9.3%, respectively, for the metabolite.

Pharmacokinetic and Statistical Analyses. Serum concentrations were analyzed by model independent methods. The maximum serum concentration (C_{max}) and T_{max} were determined by visual inspection of the data. Sumatriptan serum concentration-time profiles were considered to exhibit distinct multiple peaks if at least two consecutive concentrations between maxima were <90% of both maxima. The area under the concentration-time curve from zero to 12 hours ($AUC_{[0-12]}$) was calculated by linear trapezoidal interpolation. If the concentration at twelve hours (C_{12}) was below the quantitation limit, then C_{12} was determined by the following equation: $C_{12} = C_{last} * e^{-K*t}$, where $t = 12 - t_{last}$, and where C_{last} and t_{last} represent the last measurable concentration and the respective time. The elimination rate constant (K) and half-life (t½) were calculated from log-linear regression of the serum concentration-time profile in the terminal portion of the curve.

Total urinary recovery was determined by multiplying the concentration of parent drug (or metabolite) in urine by the volume of the urine sample in each collection interval, and calculating the sum for all intervals post-dose. Renal clearance (CLr) was calculated by dividing the total amount of parent drug (or metabolite) collected by the serum AUC over the 12 hour interval.

Pharmacokinetic parameters (AUC, C_{max}, T_{max}) were compared by ANOVA procedures (SAS, Cary, NC) between oral and jejunal administrations for both parent and metabolite. Differences were considered significant when the p-value was less than 0.05. The relationship between the sumatriptan AUC ratio (cecum/oral) and the placement of the tube (distance from the ileocecal junction, Figure 2) was determined by correlation analysis (SAS, Cary, NC).

RESULTS

All sumatriptan administrations were well tolerated by the subjects. There were no significant drug related adverse events or significant physical or laboratory changes.

Due to difficulty in positioning the oroenteric tube, the third dose was administered before the cecum in Subjects #4 (5 cm before the ileocecal junction), #5 (30 cm before the ileocecal junction), #7 (15 cm before the ileocecal junction), and #8 (61 cm before the ileocecal junction), and 35 cm past the cecum in Subject #6. Distances from the ileocecal junction were approximated from the abdominal radiograph.

Representative sumatriptan and metabolite serum concentration-time profiles (subject #2) are shown in Figure 1. Multiple peaks ($Tmax_1$ and $Tmax_2$) were observed in the sumatriptan serum concentration-time profiles for Subjects #6 (0.75 and 3.0 hr, respectively) and #8 (1.0 and 2.5 hr, respectively) after oral administration, Subject #1 (0.5 and 2.5 hr, respectively) after jejunal administration, and Subjects #1 (0.75 and 3.0 hr, respectively) and #4 (0.5 and 8.0 hr, respectively) after cecal administration.

The sumatriptan serum AUC (Table I) was not significantly different after oral and jejunal administration, but was lower after pre-cecal administration and lowest after cecal administration. The mean (SD) sumatriptan AUC ratios were: jejunum to oral = 0.90(0.18); pre-cecal to oral (4 subjects) = 0.7(0.24); and cecal to oral (4 subjects) = 0.28(0.05). Figure 2 illustrates the sumatriptan AUC ratio (cecal/oral) in relation to tube placement expressed as the distance (in centimeters) from the ileocecal junction. The extent of sumatriptan absorption progressively decreased as the site of drug delivery moved down the distal part of the the small intestine and past the ileocecal junction (Pearson R = −0.81; $p<0.05$). The metabolite AUC was significantly lower after the jejunal compared to the oral dose ($p = 0.026$). Additionally, the metabolite AUC from pre-cecal and cecal administration was considerably lower than after oral and jejunal administration. The mean (SD) metabolite AUC ratios (jejunum to oral, pre-cecal to oral, and cecal to oral) were 0.76 (0.20), 0.37 (0.10), and 0.14 (0.05), respectively. The mean (SD) AUC ratios (metabolite/parent) after oral, jejunal, pre-cecal, and cecal administration were 9.5 (3.3), 7.9 (2.4), 5.5 (2.2) and 4.4 (1.6), respectively (Figure 3).

The sumatriptan C_{max} was not significantly different after jejunal and oral administration, but was considerably lower after cecal administration. Likewise, the metabolite C_{max} was not significantly different after jejunal and oral administration but was considerably lower after pre-cecal and cecal administration. T_{max} for both sumatriptan and metabolite did not vary significantly between the sites although the range was wide for all sites of administration.

After oral administration, the mean (SD) sumatriptan elimination rate constant was 0.32 (0.09) hr^{-1} [t½ = 1.9 hr] and the CLr was 224 (27.1) mL/min. The terminal elimination rate constant could not be determined for the parent or metabolite after jejunal or cecal administration since absorption appeared to be ongoing during the later sampling times.

Approximately one-half of the oral dose was recovered in the urine as sumatriptan (3%) and metabolite (46%). The urinary recovery after jejunal and cecal administration was not calculated since metabolite was detected in the predose samples for the jejunal and cecal treatment periods, indicating carry-over from the previous dose. Furthermore, after cecal administration, only 4 subjects had urine sumatriptan concentrations above the quantitation level.

DISCUSSION

This study was conducted to determine and compare the absorption profile of sumatriptan when administered to various anatomical regions within the human gastrointestinal tract. Absorption studies are important for drugs in which an immediate therapeutic response is essential. In the case of migraine headaches, immediate and sustained relief are important criteria for therapeutic success. Knowledge of the gastrointestinal absorption characteristics of sumatriptan

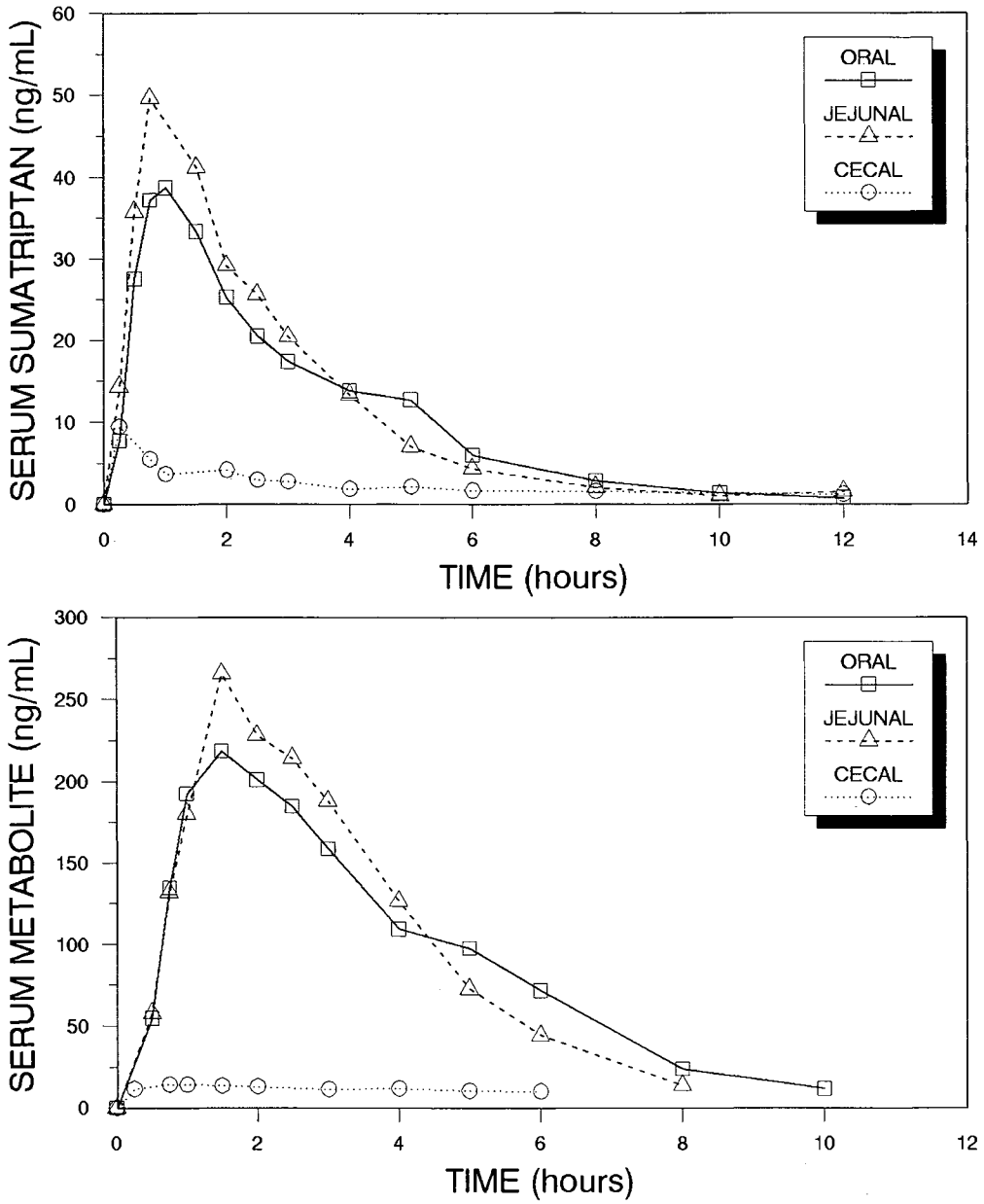

FIGURE 1: Representative sumatriptan and metabolite serum concentration-time profiles after a 50mg dose of sumatriptan.

would be essential for future optimization of therapy and dosage form development.

The sumatriptan t½ (1.9 hr) and Clr (224 mL/min) calculated after administration of the oral dose were consistent with previous studies (1-4 hr and 140-470 mL/min, respectively) [2]. Likewise, the urinary recovery of unchanged sumatriptan was consistent with other studies which suggested that approximately 50% of an oral sumatriptan dose was absorbed [2].

The AUC, C_{max} and T_{max} for sumatriptan were not statistically different after oral and jejunal administration, indicating that the rate and extent of sumatriptan absorption were similar from these sites. These results imply that sumatriptan is equally well absorbed from the stomach and jejunum, or that the majority of the absorbed dose of oral sumatriptan is absorbed in the small intestine. In contrast to sumatriptan, the metabolite AUC was statistically lower after jejunal compared to oral administration. Consequently, the AUC ratio of metabolite to parent also was statistically lower after jejunal administration (9.5 vs 7.9, respectively). The reason for these observations cannot be elucidated from the present study design but the results suggest that the extent of presystemic metabolism may be greater after oral administration. Alternatively, regional differences in the absorption of the metabolite formed within the gastrointestinal tract may contribute to or be responsible entirely for regional differences in the metabolite to parent AUC ratio. The carboxylic acid moiety of the major metabolite should exist predominantly in the ionized form at the higher pH ranges found in the human jejunum and cecum. The decreased AUC

Table I. Pharmacokinetic Parameters

Parameter[a]	Oral	Jejunal	Pre-cecal[b]	Cecal[c]
Sumatriptan				
$AUC_{[0-12]}$	117.9	108.0	77.5	35.7
(ng · hr/mL)	(16.6)	(30.4)	(33.7)	(7.6)
C_{max}	31.3	38.9	28.4	8.9
(ng/mL)	(7.4)	(10.9)	(37.4)	(6.0)
T_{max}	1.0	0.9	1.3	2.3
(hr)	(0.8–3.0)	(0.5–1.5)	(0.5–5.0)	(0.4–3.0)
Metabolite				
$AUC_{[0-12]}$	1089.6	798.7*	390.4	152.5
(ng · hr/mL)	(254.6)	(166.5)	(144.1)	(56.5)
C_{max}	227.9	197.0	69.1	17.4
(ng/mL)	(41.6)	(73.1)	(40.2)	(4.5)
T_{max}	3.0	1.8	2.3	5.0
(hr)	(1.4–4.0)	(0.8–3.5)	(1.0–5.0)	(0.8–8.1)

[a] AUC and C_{max} [arithmetic mean (SD)]; T_{max} [median (range)].
[b] Pre-cecal: dosed 5–61 cm before the cecum (n = 4).
[c] Cecal: dosed in cecum (n = 3); 35 cm past ileocecal junction (n = 1).
* $p < 0.05$; oral vs. jejunal only.

ratio of metabolite to parent in the lower regions of the gastrointestinal tract may be due to the absorbed drug bypassing the site(s) of presystemic metabolism.

In clinical studies, direct administration of drugs to specific sites in the gastrointestinal tract currently necessitates the use of relatively invasive techniques such as oroenteric intubation. Due to occasional difficulties in tube placement, these procedures, at best, approximate drug delivery to a specific region. For example, in the present study, four of the 8 subjects were dosed 5-61cm prior to the cecum, three subjects were dosed in the cecum, and one subject was dosed 35cm past the ileocecal junction. Although the original study objective was to evaluate sumatriptan absorption after administration in the cecum, the actual data collected enabled a relative comparison of the rate and extent of sumatriptan absorption from approximately 61 cm prior to 35 cm past the ileocecal junction. The mean sumatriptan and metabolite AUC and C_{max} after pre-cecal administration were more than two-fold greater than that observed after true cecal administration. Figure 2 indicates that the extent of sumatriptan absorption progressively decreased as the site of drug administration moved down the distal part of the small intestine and past the ileocecal junction. After true cecal administration, the sumatriptan AUC and C_{max} were approximately one-third that associated with oral administration. Although the range in T_{max} was large, these data suggest that the absorption phase of sumatriptan is prolonged when administered in the cecum. Sumatriptan, a weak base with pKa's > 9, should exist predominately in the ionized form throughout the gastrointestinal tract. Thus, regional differences in gastrointestinal pH would not be expected to influence sumatriptan absorption.

Metabolite (<1mg) was detected in the predose urine prior to jejunal and cecal administration. Longer washout periods were not feasible in the current study design since the timing of each dose was dependent on tube advancement. Carry-over in serum concentrations was not observed. The metabolite AUC and C_{max} were considerably lower after administration to the cecum relative to oral and jejunal administration. Furthermore, the AUC ratio of metabolite to parent was approximately two-fold lower in the cecal region. These data suggest that absorption of sumatriptan, and possibly metabolite, is decreased from the lower regions of the gastrointestinal tract, and that presystemic metabolism may not occur to a similar extent throughout the gastrointestinal tract.

In conclusion, sumatriptan was absorbed throughout the gastrointestinal tract but the extent of absorption was greater after oral and jejunal administration relative to ad-

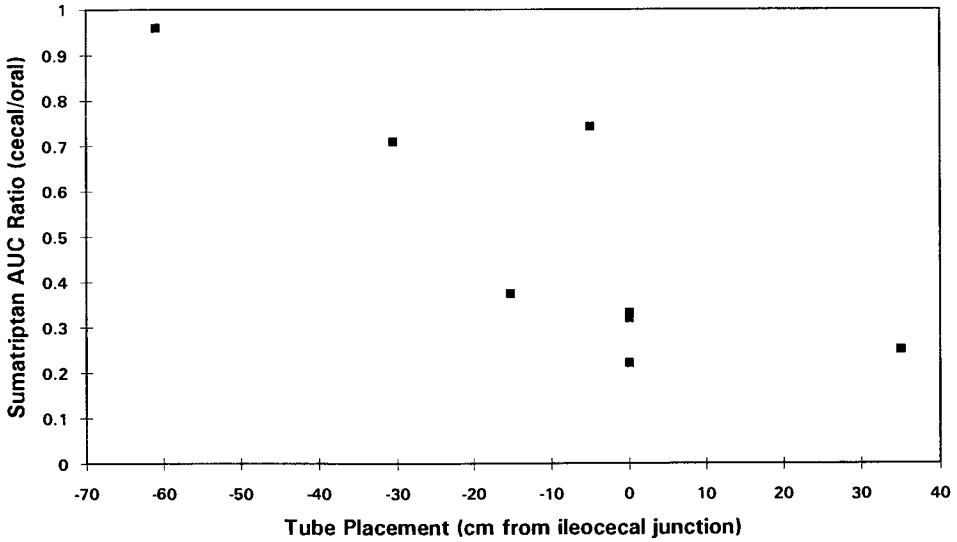

FIGURE 2: Sumatriptan AUC ratio (cecal/oral) in relation to tube placement expressed as the distance (in centimeters) from the ileocecal junction. Due to difficulty in positioning the oroenteric tube, the third dose was administered before the cecum in 4 subjects and past the ileocecal junction in one subject. Distances from the ileocecal junction were approximated from the abdominal radiograph (Pearson R = −0.81; $p < 0.05$).

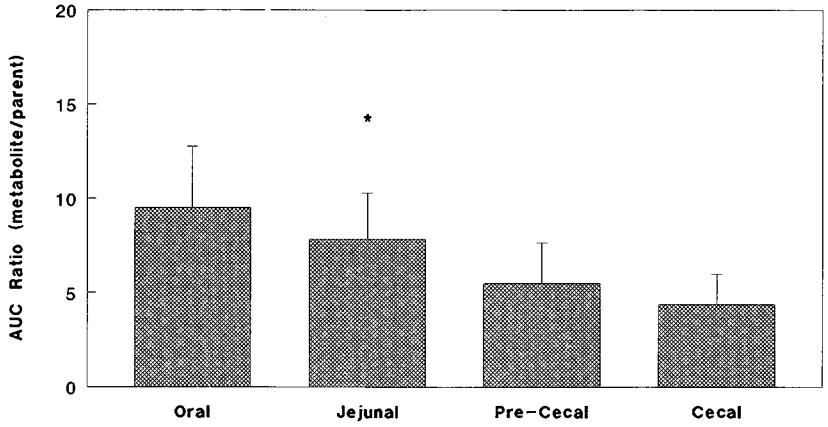

FIGURE 3: AUC ratios (metabolite/parent; mean ± SD) after oral, jejunal, pre-cecal and cecal administration of sumatriptan (50 mg). *Jejunal compared to oral administration, $p < 0.001$.

ministration in the cecal region. Additional studies are required to elucidate the influence of gastrointestinal metabolism, enterohepatic recycling, as well as other factors on the absorption of sumatriptan in the gastrointestinal tract.

ACKNOWLEDGMENTS

This work was supported in part by Public Health Service Research Grant MO1 RR00046 from the General Clinical Research Centers and Glaxo Research Institute, Research Triangle Park, NC. Patricia E. Warner was supported by a Clinical Pharmacokinetics Fellowship funded by Glaxo, Inc.

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