Absorption and Disposition of a New Antiarrhythmic Agent Bidisomide in Man

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Absorption and disposition of bidisomide were studied in 12 healthy male subjects after a 20-min iv (1 mg/kg; $N = 6$) infusion and oral (2 mg/kg; $N = 6$) administration of the ^{14}C-labeled drug. The oral absorption profile of unlabeled bidisomide was also studied after administration of a solution by a nasoenteric tube to different sites of the gastrointestinal tract (stomach, duodenum, jejunum, and ileum). The systemic availability was 61%. Absorption was slow initially and then rapid, achieving peak plasma concentrations between 2 and 4 hr. Less than complete systemic availability was attributed to incomplete absorption rather than first-pass metabolism. When the drug solution was delivered directly to the stomach, two distinct peak plasma levels were found. This was attributed to the more rapid absorption of bidisomide in the duodenum and ileum (and/or possibly colon). Following an iv dose, plasma levels of the drug declined with mean half-lives of 0.11, 2.0, and 12 hr for α, β, and γ phases, respectively, and a plasma clearance of 380 mL/min. The percentages of the dose recovered as bidisomide in urine and feces were 19 ± 1 and 29 ± 4 for the iv dose and 9.1 ± 0.9 and 48 ± 5 for the oral dose. Bidisomide did not exhibit substantial enantioselective pharmacokinetics in plasma regardless of the route of administration. The mean urinary excretion of the (−) enantiomer was, however, slightly higher than that of the (+) enantiomer, with (−)/(+) enantiomeric ratios of 1.2 and 1.3 after iv and oral administration, respectively. The enantiomeric ratio of bidisomide recovered in the feces was approximately 1.

KEY WORDS: bidisomide; absorption sites; pharmacokinetics; man.

INTRODUCTION

Bidisomide, SC-40230 (±α-[acetyl(1-methylethyl)-amino] ethyl]-α-(2-chlorophenyl)-1-piperidinebutamide) is a Class 1a/1b antiarrhythmic agent which has one chiral center (Fig. 1). It has been shown to be effective in suppressing both ventricular and atrial arrhythmia in experimental animals (1–3), suppressing premature ventricular contractions and preventing the reinduction of ventricular tachycardia in man (1). Further, bidisomide has been shown to have little effect on systemic arterial pressure in supine human subjects and to be virtually devoid of anticholinergic activity (4). The objective of the present study was to investigate the absorption and disposition of bidisomide in healthy humans.

MATERIALS AND METHODS

Materials

The following compounds were supplied by G. D. Searle & Co. (Skokie IL): [^{14}C]bidisomide, unlabeled bidisomide, (−)- and (+)-bidisomide, SC-48274A, SC-45413, and SC-43008. All other chemicals were commercially available.

Study Protocol

Pharmacokinetic Study. Twelve healthy male subjects (6 for the iv dose and 6 for the oral dose) between 18 and 45 years of age participated in the study. Prior to inclusion, subjects underwent a full medical examination and routine clinical laboratory tests of biochemistry and hematology and gave written informed consent to participate. The subjects with clinical chemistry values within the normal range were selected for the study. The dose solution of [^{14}C]bidisomide (lot No. RCT 8508; specific radioactivity, 1.34 μCi/mg) was administered to six healthy subjects over a 20-min period as an iv infusion of 1 mg/kg 1 hr after a light breakfast. Prior to and following the infusion of the drug, a 30-min iv infusion of 5% dextrose in half-normal saline (D5 1/2 NS) was given at approximately the same rate as the drug infusion rate. Lunch was taken approximately 4 hr after infusion was completed.

For the oral study each subject took approximately 200 mL of [^{14}C]bidisomide solution (lot No. RCT 8465; specific radioactivity, 1.31 μCi/mg) from a bottle supplied by the Department of Pharmaceutical Development, G. D. Searle and Co., in order to receive a dose of approximately 2 mg [^{14}C]bidisomide/kg body weight. An additional 200 mL of water was added to the bottle and each subject took the entire 200 mL of water from the bottle. The first meal was taken immediately after the 4-hr blood samples were drawn.

After iv administration, blood (5-mL) samples were taken at 0, 1, 2, 4, 6, 8, 10, 12, 15, 20, 30, and 45 min and at 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hr. Saliva samples were collected at 0, 2, 4, 6, 10, and 15 min and at 1, 2, 4, 6, 8, 12, and 24 hr. After oral administration, blood (5 ml) samples were collected at 0, 5, 10, 15, 30, and 45 min and at 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hr. The oral saliva samples were collected at 0, 5, and 15 min and 1, 2, 4, 6, 8, 12, and 24 hr. Urine samples were collected at 1, 2, 3, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hr after both iv and oral administration. Fecal samples were collected daily for 7 days after iv and oral administration. Plasma and RBCs were separated by centrifugation and frozen immediately. The saliva and fecal samples were frozen immediately upon collection. For urine samples, the volumes were measured and aliquots (approximately 100 mL) were taken upon collection. The aliquots were stored at approximately −20°C.

Absorption Site Study. This was an open-label, nonrandomized, four-way crossover study in eight healthy male volunteers. Subjects were selected according to the same criteria as described for the pharmacokinetic study. Each

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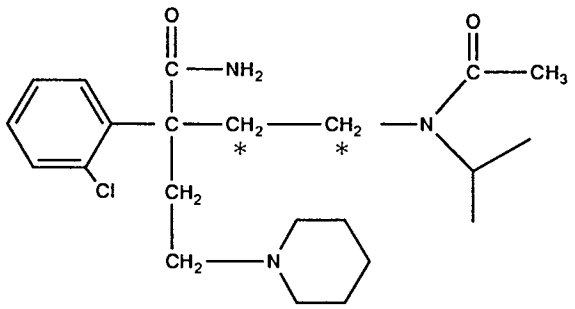

Fig. 1. Chemical structure of bidisomide. The asterisk indicates the position of labeled carbon atom.

subject received a single oral dose of bidisomide solution at 2.0 mg/kg on four separate occasions. The four doses of bidisomide were administered via a nasoenteric tube to specific sites of the gastrointestinal tract (stomach, duodenum, jejunum, and ileum). Each dose was separated by a washout period of at least 7 days. On the day before each dose, a tube was inserted through the nose into the gastrointestinal tract of each subject. The placement of the distal end of the tube in the stomach, duodenum, jejunum, or ileum was established by fluoroscopy. On the day of dosing, the exact site of the tube was confirmed by fluoroscopic examination. The dose of bidisomide solution was infused over a 30-min period. The tube remained in place until 4 hr following the dose. Subjects were in a supine position during drug administration and for at least 6 hr after drug administration. Blood samples (7 mL) were collected at 0, 10, 20, 30, and 45 min and at 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, and 24 hr after initiation of the infusion.

Plasma Protein Binding Study. The plasma protein binding of total radioactivity at 1 min and 1 and 8 hr after cessation of a 20-min iv infusion was determined using a filtration device (Amicon Co., Beverly, MA).

Sample Analysis

Total ^{14}C Concentration. Aliquots of each plasma (0.5-mL), saliva (0.5-mL), and urine (1.0-mL) sample were mixed with 15 mL of Aquassure (DuPont Co., Boston, MA) and the ^{14}C concentrations were determined by liquid scintillation counting (LSC).

Duplicate aliquots (0.3 mL) of RBC and triplicate aliquots of homogenized fecal sample were dried in CombustoCones with Combusto Pads (Packard Instruments Co., Downers Grove, IL) at room temperature and oxidized with a Packard Tri-Carb sample oxidizer (Packard Model 306, Packard Instruments Co., Downers Grove, IL). The combustion products were mixed with 9 ml of Carbosorb™ and 12 ml of Permafluor V™ (Packard Instruments Co). Total ^{14}C in the mixture was determined by LSC (Mark III, Tracor Analytic, Elk Grove, IL).

Bidisomide Concentration. Plasma concentrations of bidisomide (a mixture of (−) and (+) enantiomers) above 0.1 μg/mL were determined using a nonchiral HPLC procedure (assay range of 0.10–2.0 μg/ml) for both the pharmacokinetic study and the absorption site study. To an aliquot (0.5 mL) of plasma samples, 1 *N* sodium hydroxide solution (0.1 mL), internal standard (SC-48274A), and water (0.5 mL) were added. The mixture was placed in a SPE C8 cartridge. Bidisomide and the internal standard were eluted with HPLC mobile phase consisting of isopropanol/triethanolamine phosphate buffer at pH 5.0 (91:9, v/v).

Plasma concentrations of bidisomide in the range of 5–100 ng/mL for the pharmacokinetic study were analyzed using the following GC-MS procedure. To an aliquot (0.5 mL) of plasma, an internal standard (SC-45413), water (0.35 mL), and 1 *N* sodium hydroxide (0.05 mL) were added. The internal standard and bidisomide in plasma were extracted with 5 mL of ether. Anhydrous sodium sulfate was added to the ether layer. The diethyl ether extract was dried under a stream of nitrogen. To the dried residue, ethyl acetate (0.025 mL) and *N,O*-bis(trimethylsilyl)trifluoroacetamide (0.025 mL) were added. The vial containing the reaction mixture was sealed and heated at 80°C for 30 min and analyzed by GC-MS.

Bidisomide concentrations in the range of 25–100 ng/mL for the absorption site study were analyzed using the following GC method. To an aliquot (0.5 mL) of plasma samples, 1 *N* sodium hydroxide (0.1 mL), internal standard (SC-43008), and water (0.25 mL) were added. The mixture was placed in a Bond Elut C18 cartridge (Varian, Harbor City, CA) and the drug and internal standard were extracted with methanol (0.5 mL) after washing the cartridge with water (1 mL, two times) and dichloromethane. The methanol extracts were dried, reconstituted with toluene (0.1 mL), and injected onto a GC.

For analysis of [^{14}C]bidisomide in urine samples, an aliquot (1.0 mL) of urine samples was placed in a C18 Bond Elut cartridge (size, 1 cm^3) and radioactive materials were extracted with methanol (1.5 mL). The extracts were analyzed using an HPLRC procedure described below.

To determine the concentration of bidisomide in feces, an aliquot was pooled from each of the fecal samples proportional to its weight from 0 to 168 hr for each subject. Aliquots of pooled fecal samples (approximately 3 g) were extracted with methanol. The dried methanol extract was reconstituted in 1 mL of H_2O/methanol/1 *N* NaOH (4.0:0.2:0.1, v/v), applied to the Bond Elut column, and eluted according to the same procedure as that described for the plasma samples. The Bond Elut column eluent was analyzed using an HPLRC procedure.

For chiral separation of [^{14}C]bidisomide, [^{14}C]bidisomide was isolated from plasma and urine samples using the nonchiral HPLC procedure with the isocratic mobile phase system. From fecal samples, [^{14}C]bidisomide was isolated using the nonchiral HPLC procedure with the linear gradient mobile phase system. The isolated [^{14}C]bidisomide was analyzed using a chiral HPLRC procedure. Concentrations of (−)- and (+)-bidisomide were calculated by multiplying the fraction of each enantiomer in chiral HPLC by the respective concentration of bidisomide determined by the nonchiral HPLC and GC-MS assays.

HPLC

HPLC was performed on a Waters HPLC (Waters Associates, Milford, MA) equipped with Model 590 pumps, the Advanced Automated Sample Processor (Varian), and a reverse-phase column (Nucleosil C18, 250 × 4 mm, 10 μm)

with a UV detector at a fixed wavelength of 207 nm. Bidisomide and its internal standard were eluted with HPLC mobile phase consisting of a mixture of isopropanol/triethanolamine phosphate buffer at pH 5.0 (91:9, v/v). The flow rate of the mobile phase was 1.5 mL/min.

HPLRC

Nonchiral HPLRC was performed on a Waters HPLC equipped with Model 590 pumps, a C-18 Radial Pak liquid chromatography cartridge (8-mm ID, 10-μm particle size), WISP (Model 710B) injector, and a system controller (Model 720). For determination of bidisomide concentration in urine, an isocratic mobile phase system was used which consisted of acetonitrile and 0.01 *M* dibutylamine phosphate (25/75, by vol) at a flow rate of 1.5 mL/min. For metabolic profiles of plasma, urine, and fecal samples, a linear gradient system was employed from 5% acetonitrile in 0.01 *M* dibutylamine phosphate to 90% acetonitrile in 0.01 *M* dibutylamine phosphate over a 60-min period. The flow rate of the mobile phase was 1.5 mL/min.

Chiral HPLRC was also performed on a Waters HPLC equipped with a Chiracel AD column (Daicel Chemical Industries Ltd., Fort Lee, NJ). The mobile phase of 20/80 EtOH/hexane with 0.1% diethylamine was used at a column temperature of 40°C and a flow rate of 0.7 mL/min.

In all HPLRC assays, the radioactivity in plasma samples was detected by LSC after collection of each fraction of HPLC eluent using a Foxy fraction collector (Foxy ISCO, Lincoln, NE). The radioactivity in urine and fecal samples was determined by a Flo-One radioactive detector (Flo-One/Beta Model IC or A250, Radiomatic Instruments and Chemical Co.).

Gas Chromatography Mass Spectrometry

GC-MS was performed on a Delsi DI 700 GC equipped with a splitless injector and a FSOT DB5 column (0.25-mm id × 10 m; df, 0.25 μm) which was connected without any separator to the EI/CI source of a Nermag R3010 triple-quadrupole mass spectrometer (Delsi-Nermag S.A., Argenteuil, France). The initial temperature was set at 160°C and kept constant for 20 sec before the initiation of temperature programming. The temperature was increased at a rate of 40°C/min until it reached 220°C. After maintenance of the temperature for 1.5 min, it was increased again to 280°C at a rate of 40°C/min. The temperature of the injection port and GC-MS interface was 260°C. The mass spectrometer was operated (chemical ionization) at an ion source temperature of 120°C and a vacuum of 0.1 Torr. Selected ion monitoring of MH^+ ions was employed using the ions at *m/z* 446 and 480 for the monotrimethylsilyl derivatives of the internal standard and bidisomide, respectively.

Data Analysis

Analysis of variance was performed for each of the pharmacokinetic parameters to assess treatment differences. The statistical model included terms for subject and site of administration. If the overall *F* test for treatment differences was significant ($P < 0.05$), then multiple comparisons (Tukey's studentized range) were performed to investigate the nature of these differences.

Plasma concentration–time curves of bidisomide after iv administration of [^{14}C]bidisomide were analyzed according to a triexponential equation. The terminal elimination rate constants of bidisomide after oral administration was estimated by linear regression of the log-transformed concentrations from the terminal phase portion of the concentration–time curves. The steady-state volume of distribution (V_{dss}) was calculated using a method reported by Riegelman and Rowland (5). The other pharmacokinetic parameters were calculated as reported previously (6).

RESULTS

^{14}C Concentrations in Plasma, Red Blood Cells, and Saliva

The mean concentrations of total radioactivity in plasma, RBC (red blood cells), and saliva after iv and oral administration of [^{14}C]bidisomide are shown in Figs. 2 (A and B). Concentrations of total radioactivity in RBC were lower than those in plasma regardless of dose route. The mean AUC values of total ^{14}C in RBCs from 0 to infinity were 67 and 78% of the AUC values of total ^{14}C in plasma after iv and oral administration, respectively. Concentrations of total radioactivity in saliva were also generally lower than those in plasma and RBC after iv administration. Lower concentrations of ^{14}C in RBCs and saliva than in plasma appeared to be attributed, at least in part, to plasma protein binding of the drug. After oral administration, salivary concentrations of total radioactivity were higher than those in plasma and RBC at the early time points but lower at the later time points. The high salivary concentrations at the early time points after oral administration are most likely due to radioactivity contamination from dosing of the drug solution.

Plasma Protein Binding of Total ^{14}C. The mean percentages of plasma protein binding of total radioactivity after iv administration of [^{14}C]bidisomide were 38–39% at 1 min and 1 and 8 hr over the mean concentration range from 0.16 to 2.4 μg equiv/mL. The vast majority of plasma radioactivity was due to [^{14}C]bidisomide at 1 min and 1 hr. Thus plasma protein binding data of total ^{14}C are expected to reflect the binding of bidisomide.

Plasma Bidisomide Concentrations

The plasma concentration–time curves after iv administration of bidisomide were adequately described by a triexponential equation (Fig. 2C). The pharmacokinetic parameters are given in Table I. The mean half-lives for the α, β, and γ phases were 0.11, 2.0, and 12 hr, respectively. The apparent volume of distribution (V_d) was approximately twofold greater than the steady-state volume of distribution (V_{dss}). The substantial difference between the value of V_d and that of V_{dss} appeared to be attributed to the high elimination rate constant (K_{el}) with respect to the rate constants between the central and the tissue compartments.

After oral administration, the mean C_{max} of bidisomide (0.56 μg/mL) was achieved at 2.8 hr (Table II). The mean

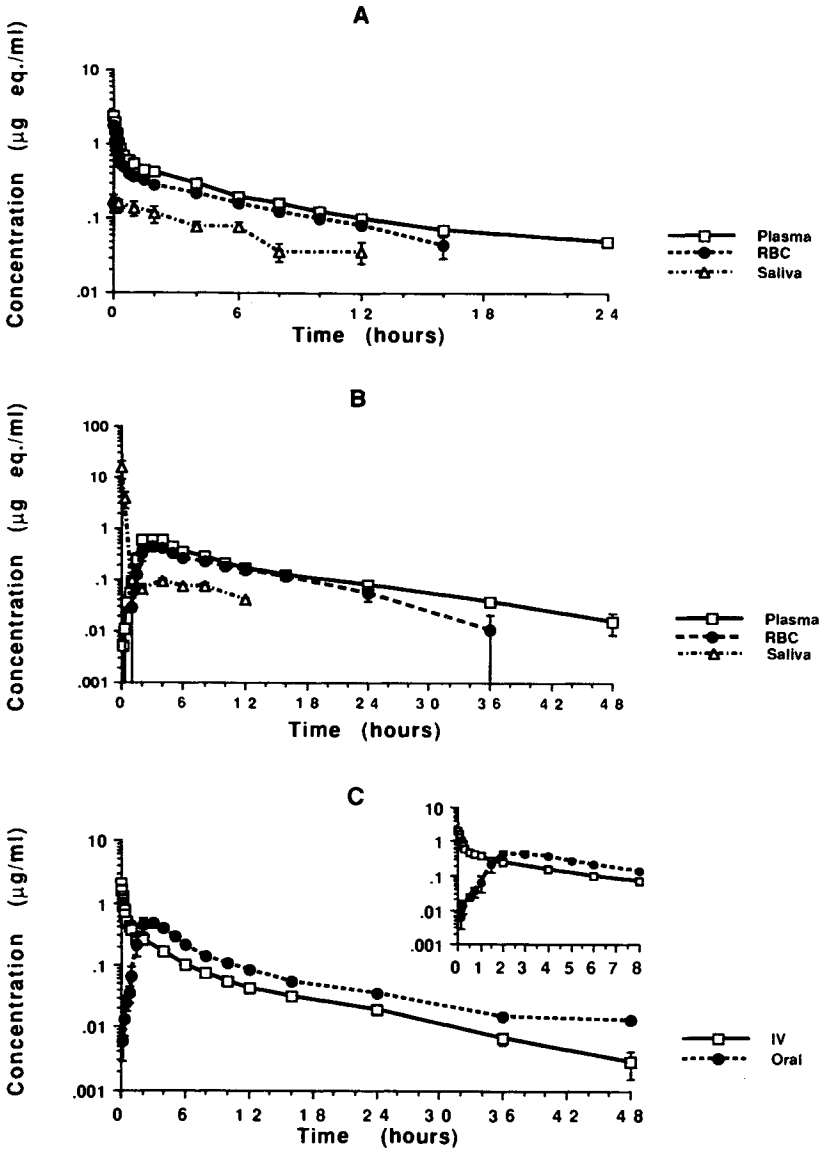

Fig. 2. Mean (±SE) concentrations of total radioactivity in human plasma, RBC, and saliva after a 20-min iv infusion of [^{14}C]bidisomide at a dose of 1 mg/kg (A) and after oral administration of [^{14}C]bidisomide at a dose of 2 mg/kg (B) and bidisomide concentrations in plasma after iv infusion and oral administration (C). The inset in C shows an expanded scale up to 8 hr. All samples were collected up to 72 hr except for saliva samples (up to 24 hr) but concentration values less than assay sensitivity are not shown.

AUC value after oral administration was approximately 61% of those for the iv dose after corrections were made for difference in doses. The terminal half-life estimated from the plasma concentration–time curve after oral administration (14 hr) was similar to that after iv administration.

The mean plasma concentrations of bidisomide after infusion of the drug to the stomach, duodenum, jejunum, and ileum are shown in Fig. 3. The mean noncompartmental pharmacokinetic parameters are shown in Fig. 4. Of these pharmacokinetic parameters, only T_{max} values were statistically different among the four treatment sites at the 5% significance level ($P < 0.05$). Results of the multiple comparisions of the T_{max} means indicated that the T_{max} for the ileum site was significantly less than the T_{max} for the stomach and duodenum sites of administration. The observed mean times to the first measurable plasma concentration (absorption lag time) for the duodenum and ileum were smaller than those for the stomach and jejunum but were not statistically significant. However, this trend appeared to be real, and significance may have been achieved with a larger sample size.

The mean plasma concentration–time curves of (−)- and (+)-bidisomide after iv or oral administration of [^{14}C]bidisomide are shown in Fig. 5. No substantial difference in plasma concentrations between the two enantiomers regardless of dose route was observed.

Table I. Pharmacokinetic Parameters of Bidisomide in Man Following an iv Dose of 1 mg/kg

Parameter	Subject No. 1	2	3	4	5	6	Mean	SD
Dose (mg)	77	65	63	66	69	80	70	7
Weight (kg)	77	66	60	67	70	77	70	7
α phase								
A^a (μg/mL)	1.8	2.3	2.3	1.9	1.6	1.7	1.9	0.3
α (hr^{-1})	7.5	8.1	7.6	5.7	5.9	5.6	6.7	1.1
α half-life (hr)	0.09	0.07	0.09	0.12	0.12	0.12	0.11	0.02
β phase								
B^b (μg/mL)	3.9	3.6	2.7	3.2	4.2	3.7	3.6	0.5
β (hr^{-1})	0.33	0.32	0.35	0.33	0.32	0.48	0.35	0.06
β half-life (hr)	2.1	2.2	2.0	2.1	2.1	1.5	2.0	0.3
γ phase								
C^c (μg/mL)	3.1	4.4	3.7	3.8	3.5	4.7	3.8	0.6
γ (hr^{-1})	0.05	0.06	0.07	0.06	0.06	0.07	0.06	0.01
γ half-life (hr)	14	12	9.6	13	11	10	12	2
MRT (hr)	8.3	8.6	6.8	8.7	7.5	7.7	7.9	0.7
AUC (μg · hr/mL)[d]	2.9	3.4	2.9	3.0	3.1	3.4	3.1	0.3
Volumes								
V_c (L/kg)	0.20	0.15	0.17	0.24	0.27	0.27	0.22	0.05
V_d (L/kg)	6.7	5.0	5.0	5.9	5.1	4.6	5.4	0.8
V_{ss} (L/kg)	2.8	2.5	2.4	2.9	2.4	2.4	2.6	0.2
Clearance (mL/min)								
Total	440	320	360	360	370	400	380	40
Renal	81	57	61	69	86	69	70	11
Urinary excretion (%)								
Total ^{14}C[e]	38	28	31	38	37	28	33	5
Bidisomide[f]	18	18	17	19	23	17	19	2
Fecal excretion (%)								
Total ^{14}C[e]	31	36	54	23	56	48	41	13
Bidisomide[f]	21	28	40	16	35	35	29	10

[a] $A = A^* (e^{\alpha T} - 1)$, where T is infusion time (0.33 hr).
[b] $B = B^* (e^{\beta T} - 1)$, where T is infusion time (0.33 hr).
[c] $C = C^* (e^{\gamma T} - 1)$, where T is infusion time (0.33 hr).
[d] Values from 0 to infinity.
[e] Values from 0 to 168 hr.
[f] Values from 0- to 168-hr pooled samples for each subject.

Urinary and Fecal Excretion of Total ^{14}C and Bidisomide

The mean percentages of total ^{14}C excreted in 0- to 168-hr urine samples after iv and oral administration are given in Tables I and II, respectively. The majority of urinary radioactivity was excreted within the first 24 hr after iv and oral administration (29 ± 2 and 14 ± 2% of the dose, respectively).

The mean percentages of the dose excreted as the parent drug in the urine over 0–48 hr after iv and oral administration were approximately 60 and 56%, respectively, of the total urinary radioactivity over the same time period. The renal clearance of total (bound plus unbound) bidisomide was approximately 60% of the creatinine clearance of normal subjects. However, after correction for plasma protein binding (39%) the renal clearance of unbound bidisomide (120 mL/min) was similar to creatinine clearance.

The percentages of total ^{14}C excreted in feces were highly variable among the subjects for both iv and oral dose groups, whereas urinary excretion of total ^{14}C was relatively consistent. The low fecal recovery of radioactivity in some subjects may be due to incomplete collection of the samples. The mean percentages of bidisomide excreted in 0- to 168-hr pooled feces after iv and oral administration were approximately 70 and 80%, respectively, of the fecal radioactivity recovered over the same time period.

The mean urinary excretion of (−) and (+) enantiomers over a 48-hr period were 10 ± 1 and 8.7 ± 0.8% of the dose, respectively, for the iv dose, and 5.3 ± 0.98 and 4.0 ± 0.6%, respectively, for the oral dose. The mean fecal excretion (0–168 hr) of (−) and (+) enantiomers were 18 ± 1 and 19 ± 1% of the dose, respectively, after iv administration.

DISCUSSION

After oral administration of 2 mg/kg [^{14}C]bidisomide to

Table II. Pharmacokinetic Parameters of Bidisomide in Man Following an Oral Dose of 2 mg/kg

Parameter	Subject No. 7	8	9	10	11	12	Mean	SD
Dose (mg)	130	140	140	140	140	120	140	10
Weight (kg)	67	70	73	72	74	63	70	4
Terminal phase								
K_e (hr^{-1})	0.05	0.06	0.05	0.06	0.07	0.03	0.05	0.01
Half-life (hr)	15	12	13	11	11	22	14	4
C_{max} (μg/mL)	0.52	0.70	0.28	0.35	0.72	0.79	0.56	0.21
T_{max} (hr)	3.0	2.0	3.0	4.0	3.0	2.0	2.8	0.8
AUC (μg · hr/mL)[a]	3.7	4.8	3.3	2.6	4.1	4.3	3.8	0.8
Urinary excretion (%)								
Total ^{14}C[b]	16	22	15	14	23	19	18	4
Bidisomide[c]	7.0	11	8.3	6.7	12	10	9.1	2.2
Fecal excretion (%)								
Total ^{14}C[b]	73	61	71	40	68	45	60	14
Bidisomide[c]	58	51	72	34	58	44	53	13

[a] Values from 0 to infinity.
[b] Values from 0 to 168 hr.
[c] Values from 0- to 168-hr pooled samples for each subject.

healthy male subjects, the systemic availability of the parent drug was approximately 61%. Less than complete systemic availability was attributed to the incomplete absorption of the drug in the gastrointestinal tract rather than extensive presystemic metabolism since the major ^{14}C labeled material in the plasma after oral administration was found to be the unchanged drug and also the ratio of total ^{14}C/unchanged drug excreted in urine was similar following the iv and oral dose.

The absorption of bidisomide receded after a lag period (up to 0.75–1.5 hr depending on subject) followed by a rapid absorption resulting in C_{max} between 2 and 4 hr (mean of 2.8 hr) following the oral dose. To explore further the mechanism of the lag period, plasma levels of bidisomide were determined in young healthy subjects in whom bidisomide was infused directly to the stomach, duodenum, jejunum, and ileum. Relative to the stomach and jejunum, the lag period prior to absorption was found to be shorter when

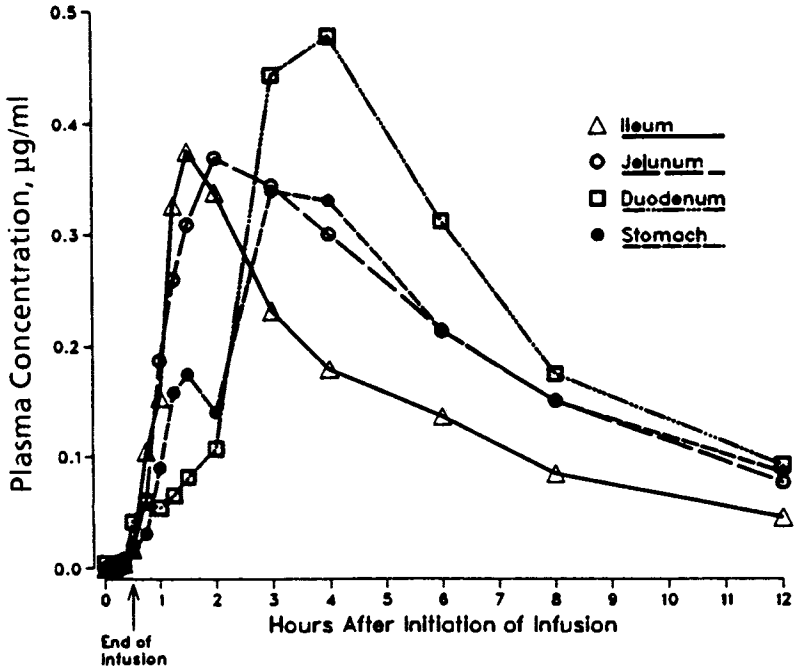

Fig. 3. Mean concentrations of bidisomide in human plasma after infusion of the drug in the duodenum, jejunum, and ileum at a dose of 2 mg/kg.

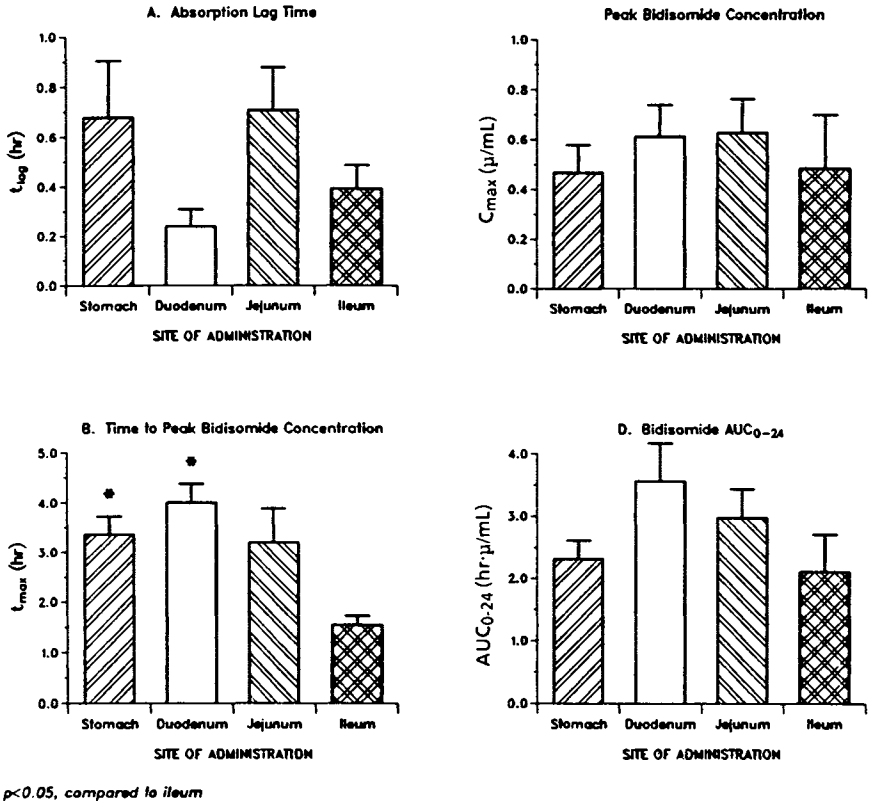

Fig. 4. Mean (±SE) pharmacokinetic parameters of bidisomide after infusion of the drug to various sites of the gastrointestinal tract.

bidisomide was administered directly into the duodenum and ileum. There was also a trend toward higher AUC values for the upper site of the gastrointestinal tract except for the stomach. These results suggest that bidisomide was absorbed at all sites with a possible exception of the stomach. However, the rate of drug absorption may be more rapid in the duodenum and ileum (and/or possibly colon). This supposition is further supported by a double-peak plasma concentration–time curve observed after bidisomide infusion to the stomach, biphasic absorption characteristics after infusion to the duodenum and the shortest T_{max} values after infusion to the ileum. The double-peak plasma concentration–time curve was also observed in some subjects after oral administration of bidisomide. This phenomenon has been reported for other drugs such as actisomide (6), pafenolol (7), penicilamine (8), cimetidine (9), renitidine (10), and veralipride (11). Two absorption sites have been postulated to explain the atypical plasma concentration–time curves of these drugs.

When bidisomide was infused to the duodenum, the distal end of the nasoenteric tube was positioned in the upper middle portion of the duodenum and the drug was not exposed to the entire duodenum. Therefore, with duodenum infusion, the residence time of the drug in the duodenum would be shorter and its duodenum absorption would be expected to be lower than with stomach infusion. This may have masked the double-peak phenomenon that was observed with stomach infusion.

Substantial absorption lag times were observed even after infusion to the ileum. This may be due to slow transport of the drug through the intestinal wall and/or due to the transit time required to reach a more optimal absorption site such as the colon. In any event, the delayed absorption observed after single-dose administration is not expected to be any disadvantage during repetitive oral dose therapy.

The terminal half-life obtained after oral administration (14 hr) was similar to that after iv administration. Thus, absorption of bidisomide was essentially complete in the elimination phase of the oral dose.

The mean volume of distribution of bidisomide (5.4 ± 0.3 L/kg) was larger than total-body volume, suggesting high uptake of the drug in the tissues. Accumulation of the drug in RBCs against the concentration gradient was not evident. Therefore, pharmacokinetic data obtained from plasma concentrations will reflect the pharmacokinetics of the drug in whole blood.

Metabolism of bidisomide was not extensive as evidenced by the fact that approximately 60 and 70% of the recovered total radioactivity in urine and feces, respectively, were the parent drug after iv administration. After oral administration, the percentages of urinary radioactivity associated with the parent drug (56%) were approximately the same as that after iv administration, indicating that there was no extensive first-pass metabolism.

Based on the recovery data of total radioactivity and bidisomide, the systemically available drug was eliminated by renal and fecal excretion, in addition to its metabolism. Excretion of radioactive materials and the parent drug was greater in feces than in urine after iv administration. These results indicate that bidisomide and its metabolites were ex-

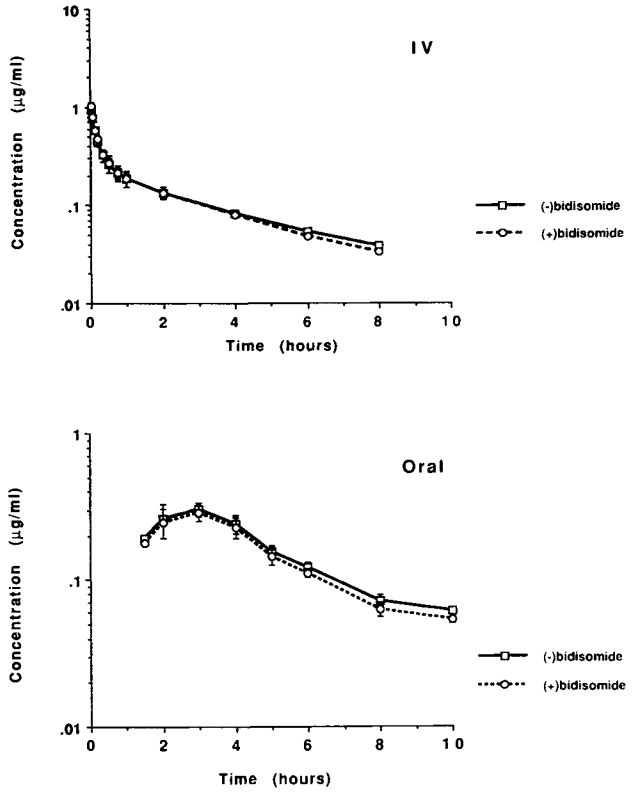

Fig. 5. Mean concentrations of (−)- and (+)-bidisomide in plasma of three selected subjects after a 20-min iv infusion of [^{14}C]bidisomide at a dose of 1 mg/kg and oral administration at a dose of 2 mg/kg.

tensively excreted in bile and/or secreted in the gastrointestinal tract. These results also indicate that nonrenal elimination was more important than renal elimination for the parent drug. These two elimination processes were equally important for the metabolites. Renal clearance of unbound bidisomide, which was similar to creatinine clearance value, suggests no substantial active reabsorption or secretion of the drug in the distal tubule.

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