Biopharmaceutics of Didanosine in Humans and in a Model for Acid-Labile Drugs, the Pentagastrin-Pretreated Dog

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Didanosine is a purine nucleoside analogue approved for the treatment of human immunodeficiency virus infection. It is extremely unstable at pH values less than 3 and requires protection against gastric acid-induced hydrolysis. Beagle dogs pretreated with pentagastrin, an analogue of gastrin that reproducibly stimulates gastric acid secretion, have been used to screen different didanosine formulations. The absolute bioavailability of didanosine from a saline solution decreased from approximately 43% in untreated dogs to 8% after pretreatment with pentagastrin. Administration of buffered solution of didanosine to untreated and pretreated dogs yielded bioavailability estimates of 37 and 30%, respectively. In humans, the bioavailability from a similar buffered solution was approximately 40%. Pentagastrin-pretreated dogs were used to evaluate four new products relative to a citrate-phosphate buffer sachet, the formulation selected for large-scale clinical trials in humans. Two of these new formulations, a chewable tablet and an antacid suspension, were more bioavailable then the reference sachet. This also proved to be true in man, necessitating an adjustment in the dose of didanosine when administered as the chewable tablet. Dogs pretreated with pentagastrin accurately predicted the improved bioavailability of new didanosine formulations prior to clinical use. This animal model may be helpful in evaluating the biopharmaceutics of other acid-labile drugs.

KEY WORDS: didanosine; pentagastrin-pretreated dog; formulation development; bioavailability.

INTRODUCTION

Didanosine (ddI; Videx) is an antiretroviral agent with activity against the human immunodeficiency virus (HIV). Didanosine requires protection against acid-induced hydrolysis in the stomach through coadministration with appropriate buffering agents (1). When didanosine is administered orally to patients as an aqueous solution with Maalox or mixed with a combination of citrate and phosphate buffers, the absolute bioavailability is approximately 40% (2). The pharmacokinetics of didanosine are linear over the range of 0.8 to 10.2 mg/kg, which includes doses of therapeutic interest (2).

The beagle dog is one of the species studied during the preclinical development of didanosine. After intravenous administration of didanosine over the range of 20 to 100 mg/kg, the pharmacokinetics of didanosine are dose dependent (3). When given orally, the absolute bioavailability of didanosine at a dose of 100 mg/kg is 46% (4). The bioavailability of didanosine from a sodium acetate buffer solution ranges from 43 to 48% over a dose range of 50 to 250 mg/kg (5). The published data (2–4) suggest that the pharmacokinetic profile of didanosine in the dog is similar to that in man in many respects, including rapid absorption and elimination, distribution primarily in total-body water, comparable estimates of absolute bioavailability for a buffered solution, and evidence of active renal tubular secretion in both species.

During the didanosine Phase I and II clinical program, several changes in formulation were made. In order to screen formulations prior to clinical evaluation, the dog was developed as a model. Since the pH of the contents of the dog stomach can range from 0.8 to 8 (6), animals were pretreated with pentagastrin prior to dosing with didanosine. Pentagastrin, an analogue of the natural hormone gastrin, causes a rapid and reproducible decrease in gastric pH (6,7). The present studies describe the use of the pentagastrin-pretreated dog as a model for the evaluation of new didanosine formulations.

MATERIALS AND METHODS

Dosage Forms

Six formulations of didanosine were utilized in studies conducted in beagle dogs or humans. The first formulation given to dogs consisted of a buffered solution containing 0.45 *M* sodium phosphate dibasic and 0.30 *M* sodium citrate dihydrate, pH 9.0. Subsequently, a citrate–phosphate buffer sachet formulation was developed for clinical use, which contained, in addition to 250 or 375 mg of didanosine, sodium citrate USP dihydrate, dibasic sodium phosphate anhydrous, citric acid, and 14.5 g sucrose. The total weight of a unit dose was 20 g, and it reconstituted to form a solution with a pH of approximately 7.5. Later formulations included a chewable tablet, an antacid suspension, an electrolyte solution, and a compression-coated tablet. The chewable tablet formulation contained 125 or 150 mg of didanosine, dihydroxyaluminum sodium carbonate, magnesium hydroxide, sodium citrate, and sucrose. Each tablet weighed 3 g. The antacid suspension formulation contained approximately the same ingredients, both qualitatively and quantitatively, as two chewable tablets. Reconstitution of this formulation with water resulted in the formation of a solution of didanosine, although the antacid components remained in suspension. The electrolyte solution formulation, used only in dogs, contained 250 mg didanosine, sodium and potassium bicarbonate, sodium and potassium citrate, and sucrose. The compression-coated tablet product, also administered only to dogs, contained a core of didanosine (approximately 83 mg per tablet) mixed with microcrystalline cellulose, sur-

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rounded by sodium bicarbonate, aluminum hydroxide, and magnesium carbonate.

Studies in Beagles

Design of Study 1

A three-way randomized crossover design was employed to evaluate the absolute bioavailability of didanosine from two solutions after oral administration of a 50 mg/kg dose to three adult male beagle dogs. Each dog received an intravenous dose of didanosine over 5 min, administered at the rate of 0.5 mL/min/kg using a calibrated infusion pump. The intravenous solution was prepared in sterile 0.9% sodium chloride and filtered through a 0.22-μm filter. The oral doses of didanosine were administered by gavage as solutions prepared in 0.9% sodium chloride or the pH 9.0 buffer in a volume equivalent to 3.5 mL/kg. After the completion of the initial three treatments, the same dogs received the oral doses after pretreatment with pentagastrin (Peptavlon), delivered intramuscularly at a dose of 6 μg/kg 20 min prior to dosing with didanosine. Dogs were fasted overnight before and for 6 hr after dosing. There was a minimum recovery period of 1 week between sessions.

Dogs were restrained in fabric restraint slings for the first 6 hr after dosing. A 3-mL sample of blood was collected into a heparinized Vacutainer prior to dosing and at 3, 6, 9, 12, 15, 21, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, and 10 hr after the intravenous dose and at 10, 20, 30, and 45 min and 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 hr after each oral dose. Blood samples were obtained either from a saphenous vein catheter or via jugular venipuncture. Plasma was prepared within 60 min of sample collection, then stored at −20°C. Catheterized urine samples were obtained predose and over the intervals 0 to 1, 1 to 2, 2 to 3, 3 to 4, and 4 to 6 hr after dosing. After the 6-hr sample, the dogs were transferred to stainless-steel metabolism cages. Two additional urine samples were obtained over the intervals of 6 to 10 and 10 to 24 hr by collecting whatever urine was voided in the cage tray, which drained into a polypropylene container held on ice. The cage was rinsed with approximately 50 mL of water to ensure a complete collection of the voided urine at the end of each interval. After the total volumes of the urine and rinse water were recorded, an aliquot of urine was mixed with 0.02 *M* potassium phosphate buffer (pH 8.0), 1 part urine to 2 parts buffer. The buffered urine samples were stored at −20°C until analysis.

Design of Study 2

A five-way randomized crossover was conducted in five adult male beagle dogs to evaluate the bioavailabilities of four oral formulations of didanosine, relative to that from the citrate–phosphate buffer sachet used in human studies. Each dog was pretreated with pentagastrin as described in Study 1. A 250-mg dose of each formulation was given after an overnight fast. The four test products administered were the chewable tablet, antacid suspension, electrolyte solution, and compression-coated tablet. Two chewable tablets (125 mg didanosine per tablet) were ground to 20 mesh and mixed with 120 mL of water. The citrate–phosphate buffer, antacid suspension, and electrolyte solution were reconstituted with 120 mL of water prior to administration. Each of these four formulations was administered by gavage, and the gavage tube was rinsed with 20 mL of water prior to removal from the stomach. For the compression-coated tablet, three tablets were given in rapid succession following gavage administration of 140 mL of water. One week elapsed between treatments.

Serial blood samples were collected using jugular venipuncture into heparinized Vacutainers prior to dosing and at 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, and 8 hr after dosing. The total urine output from each dog was collected over a 24-hr interval into the cage tray and processed as described in Study 1. Plasma and buffered urine samples were stored at −20°C until analysis.

Studies in Humans

Design of Study I

Based upon their superior bioavailability in the second study conducted in dogs, the chewable tablet and antacid suspension formulations were selected for evaluation in humans. A randomized three-way crossover study, balanced for first order residual effects, was conducted in 18 male patients, using the citrate–phosphate sachet as the reference product. The patients were seropositive for HIV but did not have any symptoms of AIDS or AIDS-related complex. In addition, patients were excluded from the study if there was any evidence of hepatic or renal dysfunction. Patients signed the appropriate informed consent documents prior to any study procedures. The mean (SD) age, body weight, and height of the patients were 31 (3) years, 77.1 (10.1) kg, and 178.6 (6.5) cm, respectively.

Each patient received a single 375-mg dose of each of the three didanosine formulations. Patients were required to fast for 10 hr prior to dosing and for 4 hr after drug administration. There was a 1-week washout period between sessions. The tablets were chewed in rapid succession, followed by a rinse and gargle with 120 mL of room-temperature tap water. The sachet and suspension formulations were reconstituted with 120 mL of water, then swallowed immediately. Serial heparinized blood samples were collected prior to and at 0.15, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, and 10 hr after dosing. The total urine output, collected as discrete intervals, was obtained predose, 0 to 4, 4 to 8, and 8 to 12 hr after dosing. The collection bottles were kept in a refrigerator except during voiding. At the end of each interval, the total volume of the urine was measured and recorded. The urine sample was mixed thoroughly and a 2-mL portion of the sample was transferred to a polypropylene tube containing 4 mL of 0.20 *M* potassium phosphate buffer, pH 8.0. Plasma and urine samples were stored at −20°C prior to analysis.

Design of Study II

Since the bioavailability of didanosine from the chewable tablet was greater than that from the buffered sachet, a second bioequivalence study was conducted. In Study II, the dose of the chewable tablet formulation was 20% lower than the dose of the citrate–phosphate buffer sachet. Twenty-four male patients seropositive for HIV were enrolled using a randomized two-way crossover design. The

inclusion and exclusion criteria for this study were identical to those for Study I. Patients had a mean (SD) age of 31 (5) years, an average body weight of 72.7 (8.3) kg, and a mean height of 176.5 (7.1) cm.

Each patient received a single 300-mg dose of didanosine, formulated as two 150-mg chewable tablets, and a 375-mg dose of the citrate–phosphate buffer sachet. One week elapsed between successive treatments. Five milliliters of heparinized blood was collected predose and at 0.15, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hr after dosing. The total urine output was collected at predose and over the intervals of 0 to 4, 4 to 8, and 8 to 12 hr after dosing. Plasma and urine samples were stored at −20°C until analysis.

Analyses of Biological Fluids

Plasma and urine samples collected from dogs and humans were analyzed for didanosine using HPLC/UV methods (3,8). Data from standards, prepared in the appropriate matrix, were fit to a linear regression equation by weighting each standard by the reciprocal of its concentration and testing for outliers by the method of Prescott (9). The concentration of didanosine in each study sample was derived by inverse prediction from the regression line. Quality control samples, consisting of control matrix from each species spiked with known concentrations of didanosine, were included in each analytical sequence to verify the accuracy and precision of the analyses, as well as to document the stability of didanosine during sample storage.

The standard curves for the quantitation of didanosine in dog and human plasma were linear over the range of 25 to 10000 ng/mL. In urine, the curves were linear over the ranges of 2 to 500 μg/mL (dog) and 1 to 400 μg/mL (human). The within- and between-day precision estimates for quality control sample concentrations distributed across the range of the standard curves generally did not exceed 6 and 7% relative standard deviation (RSD), respectively, for dog or human plasma analyses. For urine samples, the within- and between-day precision values did not exceed 10% RSD. Mean observed concentrations of didanosine in plasma or urine quality control samples from both species were within 10% of the nominal concentration values. These data indicate that the assays for didanosine in plasma and urine were accurate and precise, in addition to demonstrating the stability of didanosine under the conditions used to store the study samples.

Pharmacokinetic Analysis

The didanosine plasma concentration-versus-time data were analyzed using noncompartmental and statistical moment methods (10,11). The terminal elimination rate constant, λ, was derived from the absolute value of the terminal slope of the log-linear portion of the plasma profile. The log-linear phase was defined by a minimum of three of the last n data points (ln$C$, t), where "n" was selected to minimize the mean square error. The apparent elimination half-life, $t½$, was calculated by the equation 0.693/λ. The area under the plasma concentration-versus-time curve (AUC) and the area under the first moment curve (AUMC) were calculated using a combination of trapezoidal and log trapezoidal methods (11). AUC and AUMC were extrapolated to infinity and reported as $AUC_{0-\infty}$ and $AUMC_{0-\infty}$. The mean residence time (MRT) was estimated using the standard methods (11). Renal clearance, CL_R, was calculated by dividing the amount of didanosine recovered in the urine by the $AUC_{0-\infty}$. Since the renal clearance of didanosine appeared to vary with the route of administration, the absolute bioavailability, F, of didanosine in the dog was determined using the Kwan–Till method (12) according to the equation

$$F = \frac{AUC_{po} D_{iv}(1 - f_{u,iv})}{AUC_{iv} D_{po}} + f_{u,po}$$

where f_u is the fraction of administered dose that is excreted unchanged in the urine, D is the dose, and the subscripts indicate the route of administration. The peak plasma concentration (C_{max}), the time at which C_{max} occurred, T_{max}, and the cumulative percentage of the dose recovered in the urine as didanosine, UR, were obtained directly from the experimental data.

Statistical Analyses

Due to the limited number of animals in Study 1, the pharmacokinetic data were summarized but were not statistically evaluated. Analysis of variance models appropriate for the particular study design were used to evaluate data from Study 2 in the dogs and both of the clinical trials. For Study 2 in dogs, a randomized block analysis of variance was performed. For clinical Studies I and II, analysis of variance for a three-way and two-way crossover study was performed, respectively.

In the clinical studies, the bioequivalence assessments of the chewable tablet and/or suspension formulations of didanosine relative to the citrate–phosphate buffer sachet were made on the basis of the two one-sided tests procedure discussed by Schuirmann (13). Based on C_{max} and $AUC_{0-\infty}$ values, two formulations were considered equivalent if the 90% confidence limits of the difference between the two means were contained within 80 to 120% of the reference formulation mean. If the analysis was performed using the log-transformed data, the antilogs of the limits for the difference between the log means provided the confidence limits of interest.

All statistical calculations and tests were performed using the SAS package (14). A P value of 0.05 was used as the significance level for all tests.

RESULTS

Studies in Dogs

The mean (SD) pharmacokinetic parameter values for didanosine after intravenous and oral administration to dogs in Study 1 are summarized in Table I. The mean plasma concentration-versus-time profiles after oral administration are shown in Fig. 1. Didanosine is rapidly absorbed after oral dosing, reaching peak plasma concentration values within 45 min. Elimination was also rapid, with an apparent $t½$ of 0.71 hr after an intravenous dose. The absolute bioavailability, estimated using the Kwan–Till method, averaged 37 or 43% for a buffered or saline solution, respectively. When dogs were pretreated with pentagastrin, the mean bioavailability

Table I. Mean (SD) Pharmacokinetic Parameters of Didanosine After the Administration of a Single 50-mg/kg Intravenous or Oral Dose to Three Beagle Dogs

Treatment description[a]	C_{max} (μg/mL)	T_{max} (hr)[b]	MRT (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (μg · hr/mL)	CL_R (mL/min)	UR (%)	F (%)
Intravenous	144.7[c]	0.10	0.72	0.71	52.9	85	39.2	—
	(38.5)		(0.10)	(0.08)	(13.2)	(54)	(9.6)	
Saline solution	26.0	0.33	1.17	0.88	22.1	97	17.9	43
	(19.1)	(0.33–0.50)	(0.12)	(0.09)	(14.0)	(43)	(8.9)	(23)
Buffered	12.4	0.75	1.39	1.22	14.4	163	20.2	37
solution	(3.1)		(0.19)	(0.39)	(6.2)	(118)	(8.6)	(11)
Pentagastrin–	3.0	0.33	1.04	0.92[d]	2.8	182	5.1	8
saline	(2.2)	(0.33–0.50)	(0.34)		(2.2)	(86)	(5.7)	(8)
Pentagastrin–	9.1	0.50	1.81	1.99	9.4	201	19.0	30
buffer	(3.2)	(0.33–0.50)	(0.17)	(0.63)	(1.5)	(161)	(14.1)	(17)

[a] Intravenous dose given as a 5-min constant-rate infusion. All other treatments were given orally by gavage. Dogs were pretreated with pentagastrin 20 min prior to the administration of didanosine in two dosing sessions.
[b] Median (minimum–maximum) reported. If no range is present, then all values are the same.
[c] Corresponds to the first sample collected after the end of infusion.
[d] Insufficient number of quantifiable points for the calculation of $t_{1/2}$ in one dog.

decreased to 8% for the saline solution, while bioavailability from the buffered solution remained relatively stable at 30%.

In the second study in dogs, there were significant differences in the relative bioavailabilities of five different formulations of didanosine, as shown in Table II. Concentration-versus-time profiles for three of the formulations evaluated in the dog are compared to the profiles obtained in humans after administration of the same formulations in Fig. 2. C_{max} values for the antacid suspension, chewable tablet, and compression-coated tablet were significantly different from the C_{max} for the citrate–phosphate buffer sachet, averaging 149, 197, and 118% greater than the value for the sachet, respectively. C_{max} values for the electrolyte solution were not significantly different from the citrate–phosphate buffer. Absorption of didanosine was rapid from all five formulations, with T_{max} consistently occurring at 0.75 hr or less. $AUC_{0-\infty}$ values for the antacid suspension and the chewable tablet were significantly greater than those observed for the sachet, averaging 35 and 47% more than the value for the reference product, respectively. The $AUC_{0-\infty}$ values for the sachet, the electrolyte solution, and the compression-coated tablet were not different. No statistically significant differences among the formulations were observed with respect to $t_{1/2}$ or CL_R.

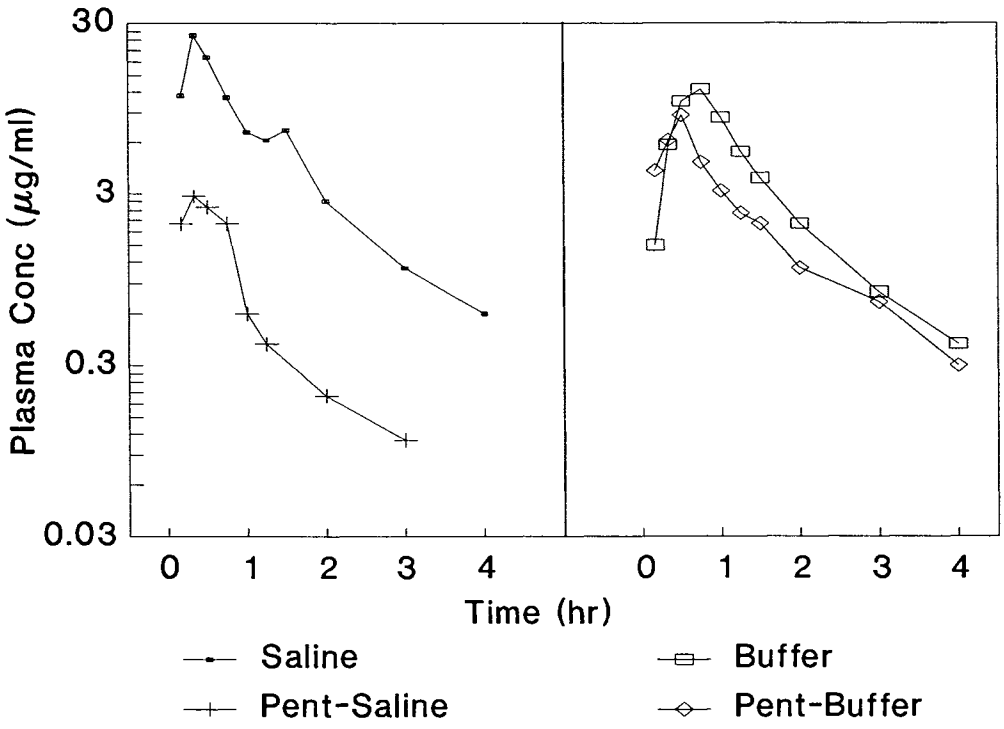

Fig. 1. Mean plasma concentration-versus-time profiles for didanosine after the administration of single 50-mg/kg oral doses to three beagle dogs.

Table II. Mean (SD) Pharmacokinetic Parameter Values of Didanosine After the Administration of a Single 250-mg Dose of Five Formulations to Five Dogs Pretreated with Pentagastrin

Treatment description (No.)	C_{max} (ng/mL)	T_{max} (hr)[a]	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (hr · ng/mL)	CL_R (mL/min)	UR (%)
Citrate–phosphate buffer sachet (1)	4,747 (720)	0.75 (0.50–1.0)	0.68 (0.14)	6,283 (760)	116 (14)	17.6 (3.0)
Electrolyte solution (2)	7,005 (1,042)	0.50	0.73 (0.16)	7,767 (1,035)	106 (24)	19.3 (2.7)
Antacid suspension (3)	11,819 (2,908)	0.35 (0.25–0.50)	0.74 (0.10)	8,471 (1,409)	106 (13)	21.3 (1.3)
Chewable tablet (4)	14,100 (779)	0.25	0.74 (0.13)	9,245 (1,143)	103 (24)	22.6 (4.9)
Compression-coated tablet (5)	10,361 (1,687)	0.50	0.91 (0.17)	7,800 (797)	107 (27)	19.6 (3.4)
Tukey lines*	1 2 5 3 4	ND[b]	NS[c]	1 2 5 3 4	NS	ND

[a] Median (minimum–maximum) reported. If no range is present, then all values are the same.
[b] Statistical analysis not performed.
[c] No statistically significant differences observed.
* Means not connected by a common underline are significantly different, $P < 0.05$.

Studies in Humans

The pharmacokinetic data from Study I, the initial bioequivalence study, are summarized in Table III. Didanosine reached peak plasma concentrations within 0.25 to 1.5 hr after dosing, and median T_{max} values were very similar for the three formulations. There were no significant differences among treatments with respect to MRT, $t½$, or CL_R. There were, however, significant differences in the extent of absorption, as evidenced by C_{max} and $AUC_{0-\infty}$ values. The mean C_{max} values for the chewable tablet and antacid suspension were 20 and 36% greater than the mean value for the citrate–phosphate buffer sachet, respectively. For $AUC_{0-\infty}$, the chewable tablet mean value was 16% and the antacid suspension value 25% greater than the value observed for the sachet. As shown in Table III, since the 90% confidence intervals for C_{max} and $AUC_{0-\infty}$ for the chewable tablet and suspension formulations, relative to the citrate–phosphate buffer sachet, exceeded the upper boundary of 120%, it was concluded that neither of these products was equivalent to the reference sachet.

The second bioequivalence study conducted in humans, Study II, was designed to demonstrate that a reduced dose of the chewable tablet would produce systemic exposure simi-

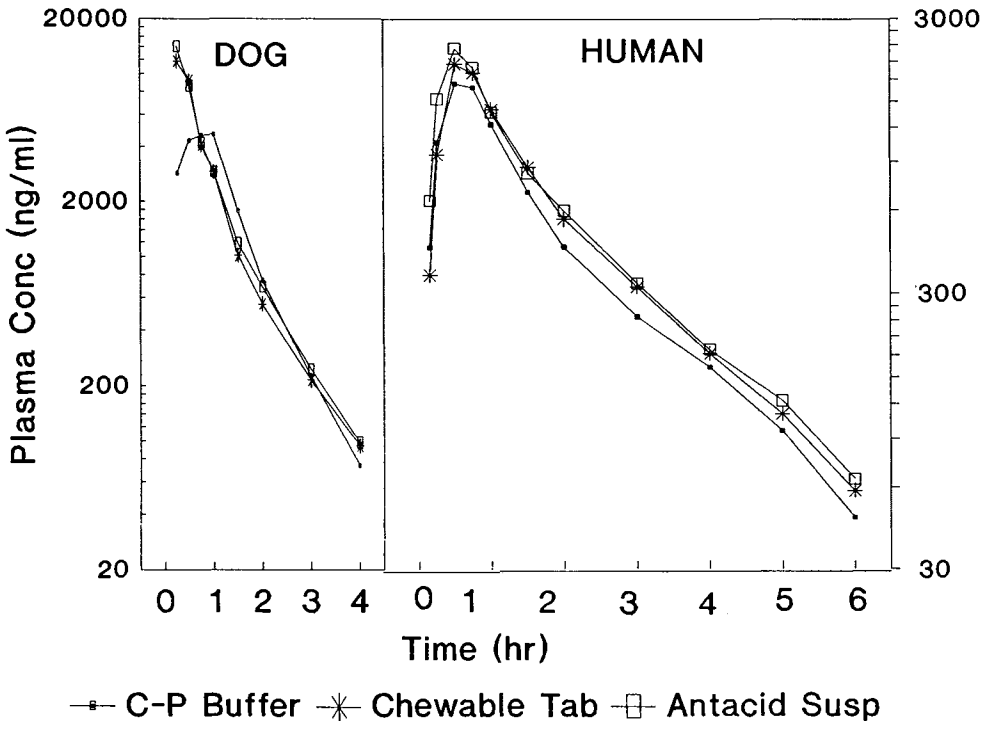

Fig. 2. Mean plasma concentration-versus-time profiles for didanosine in five beagle dogs given a 250-mg dose and in 18 humans after the administration of a 375-mg dose of three formulations.

Table III. Mean (SD) Pharmacokinetic Parameters of Didanosine After the Administration of a Single 375-mg Oral Dose of Three Formulations to Eighteen Patients Seropositive for HIV

Treatment description	C_{max} (ng/mL)	T_{max} (hr)[a]	MRT (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (hr · ng/mL)	CL_R (mL/min)	UR (%)
Citrate–phosphate buffer sachet	1901 (472)	0.68 (0.50–1.00)	1.77 (0.27)	1.36 (0.47)	2851 (673)	507 (149)	21.9 (6.7)
Chewable tablet	2364 (977)	0.50 (0.25–1.50)	1.86 (0.32)	1.37 (0.39)	3315 (877)	455 (108)	23.0 (4.5)
Antacid suspension	2651 (877)	0.50 (0.50–0.75)	1.80 (0.35)	1.39 (0.23)	3574 (807)	477 (91)	26.4 (5.9)
Relative bioavailability estimate (%)[b]							
Chewable tablet	120	ND[c]	105	102	116	90	105
Antacid suspension	136	ND	101	106	125	94	120
90% confidence interval (%)							
Chewable tablet	106, 135	ND	96, 114	89, 116	108, 125	82, 98	94, 115
Antacid suspension	121, 154	ND	93, 110	93, 120	117, 134	86, 102	110, 131

[a] Median (minimum–maximum) reported.
[b] Point estimate and 90% confidence interval based on the analysis of log-transformed data for C_{max}, MRT, and $t_{1/2}$.
[c] Statistical analysis not performed.

lar to that achieved with the recommended dose of the citrate–phosphate buffer sachet. Mean pharmacokinetic parameter values, as well as the 90% confidence interval data for the comparison of the chewable tablet and citrate–phosphate buffer sachet, are summarized in Table IV. A 20% decrease in the dose of the tablet, relative to the sachet, resulted in very similar C_{max} and $AUC_{0-\infty}$ values. In agreement with the previous study, there were no significant differences between the two formulations in MRT, $t½$, or CL_R values.

DISCUSSION

Drugs undergoing development for the treatment of HIV infection require rapid clinical evaluation once initial assessments of *in vitro* and *in vivo* activity and preclinical toxicity suggest a new agent shows therapeutic promise. In the case of didanosine, this accelerated time frame resulted in the initiation of Phase I trials with a formulation that was not suitable for commercial use. The development of an acceptable oral formulation was further complicated by the instability of didanosine in an acidic environment, as demonstrated by previous studies in which the rate of decomposition was approximately 5%/min at 37°C and a pH of less than 3 (1). Since many antacid products capable of protecting didanosine from hydrolysis were available in a variety of combinations, it was necessary to develop an animal model to serve as a screening tool. The pharmacokinetics of didanosine in the dog are similar to those in humans (2–4), and the dog is a convenient species in which to perform multiple-leg crossover studies. Gastrointestinal motility in the dog is also similar to humans, including the rate of emptying of liquids from the stomach (15).

The pH of the gastric contents in a fasting dog may range between 0.8 and 8, with a majority of animals having a basal pH greater than 2 (6). The average gastric pH in the dog has also been reported to be slightly greater than the value in man (16), which has been attributed to the lower rate of basal acid secretion in the dog (17). This variability in gastric pH, coupled with a lower basal acid output, may explain why the bioavailability of didanosine in the dog was not improved by administration in a buffered vehicle. However, once gastric acid secretion was stimulated with pentagastrin, the bioavailability from a buffered solution remained relatively unchanged, while the bioavailability from a saline solution decreased dramatically. Although there have been

Table IV. Mean (SD) Pharmacokinetic Parameters of Didanosine After the Administration of a Single 300-mg Dose of the Chewable Tablet or a 375-mg Dose of the Citrate–Phosphate Buffer Sachet to Twenty-Four Patients Seropositive for HIV

Treatment description	C_{max} (ng/mL)	T_{max} (hr)[a]	MRT (hr)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (hr · ng/mL)	CL_R (mL/min)
Citrate–phosphate buffer sachet	1649 (628)	0.75 (0.50–1.00)	2.32 (0.78)	1.73 (0.81)	3006 (859)	455 (171)
Chewable tablet	1628 (536)	0.50 (0.25–1.00)	2.17 (0.58)	1.71 (1.01)	2557 (759)	430 (166)
Relative bioavailability estimate (%)	101[b]	ND[c]	95[b]	97[b]	84[b]	95
90% confidence interval (%)	92, 110		89, 101	87, 108	78, 91	84, 106

[a] Median (minimum, maximum) reported.
[b] Point estimate and 90% confidence interval based on the analysis of log-transformed data.
[c] Statistical analysis not performed.

no controlled studies to evaluate the bioavailability of didanosine from a nonbuffered solution in humans, it is reasonable to expect that it will be decreased relative to a solution with adequate acid neutralizing capacity, since humans do maintain a basal rate of acid secretion (18).

Antacids suitable for use in didanosine formulations were selected based upon their ability to increase gastric pH as well as their acid neutralizing capacity. Prospective formulations were required to increase the pH of a simulated gastric environment to 5 and maintain this value for 1 hr. There were, however, differences among the chewable tablet, antacid suspension, and citrate–phosphate buffer with respect to acid neutralizing capacity, which averaged 43 mEq per tablet, 66 mEq per unit dose of the suspension, and 34 mEq per unit dose of the sachet. Both the tablet and the suspension contain a combination of a soluble antacid, designed to buffer the gastric juice immediately; and insoluble antacids, which provide for sustained neutralization. The sachet contains only soluble buffers. Differences in antacid composition may contribute to the observed increase in bioavailability from the tablet and suspension, relative to the sachet.

The chewable tablet and antacid suspension were selected for clinical evaluation primarily because they exhibited improved bioavailability in the pentagastrin-pretreated dog. This characteristic was subsequently confirmed in the first human bioequivalence study comparing the tablet, suspension, and sachet. The chewable tablet was subsequently chosen for commercialization, since it offers several advantages over the citrate–phosphate buffer sachet. The tablets are more convenient to administer, since they can be chewed or dispersed in a small volume of water. Each tablet weighs approximately 3 g, which is considerably lighter than the 20-g weight of the sachet. Finally, the dose of didanosine may be reduced approximately 20% when it is administered as the tablet and still achieve exposure equivalent to that from the sachet, as demonstrated in the second bioequivalence study.

Pretreatment with pentagastrin dramatically decreased the bioavailability of didanosine from a nonbuffered solution, suggesting that studies in dogs with stimulated gastric acid secretion might be useful in evaluating the protective abilities of different antacid combinations. The dog model allowed the rapid selection of two formulation candidates which demonstrated bioavailability superior to that from a didanosine product already in clinical use. The data in the dog were corroborated by studies in humans, resulting in the ability to decrease the dose of didanosine without adversely effecting exposure to the drug. Although the gastric pH of the dogs was not measured, other investigators have demonstrated that the dose of pentagastrin used in the present study reliably and uniformly increases gastric acidity (6). In 23 dogs, which initially had gastric pH values ranging from 0.8 to 8, pH values within the range of 1 to 2 were attained 15 min after administration of pentagastrin. This effect persisted for up to 60 min after dosing, the last time point evaluated, when the measured pH values ranged from 0.9 to 1.1. To ensure maximal stimulation of gastric acid production in the dogs we studied, we administered didanosine 20 min after pentagastrin. The use of pentagastrin as a pretreatment in the dog may offer advantages in the study of other acid-labile drugs or agents dependent upon an acidic pH for absorption.

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