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Oral Absorption of CGS-20625, an Insoluble Drug, in Dogs and Man

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Oral bioavailability of highly water-insoluble drugs is often quite limited and variable, requiring the development of improved formulations. Animal models are an essential aspect of the design and testing of such formulations designed to improve absorption in man. The present report compares the absorption of CGS-20625, an insoluble drug, in dog and man after oral administration of the drug as a powder, a solid dispersion capsule, and after gastric and duodenal administration in PEG 400 solution. CGS-20625 powder (20 mg) given orally exhibited slow, delayed absorption in both dog and man, with a C_{max} of 0.26 ± 0.07 μg/ml at T_{max} of 3 hr in dog, and 0.01 ± 0.004 μg/ml at 2 hr in man. Administration of CGS-20625 in PEG 400 solution improved absorption in dog and man, with a C_{max} of 1.2 ± 0.10 μg/ml at T_{max} of 0.25 hr in dog, and a C_{max} of 0.10 ± 0.04 μg/ml at 0.5 hr in man. T_{max} after administration of the hard gelatin capsule formulation was 0.9 and 1.0 hr in dog and man, with C_{max} of 0.89 ± 0.16 and 0.052 ± 0.014 μg/ml, respectively. Absolute bioavailability of CGS-20625 powder in the dog was 0.67 ± 0.21, whereas the bioavailabilities of the powder and the capsule relative to the PEG 400 solution were 0.84 and 1.1, respectively, in dog, and 0.41 and 0.85 respectively, in man. No significant benefits of duodenal administration were observed. Plasma levels were approximately 10-fold greater and oral clearance was approximately 5-fold less in the dog than in man. Furthermore, pharmacokinetic data were less variable and relative bioavailability was greater in dogs than in humans. Physiological factors in the gastrointestinal tract or greater first-pass metabolism in man may account for these species differences. The relative rate and extent of CGS-20625 absorption were similar between dog and man, in the order of powder < capsule < PEG 400 solution. In addition, in vivo *absorption rates in both species reflect* in vitro *dissolution differences between the powder and the capsule. These data strongly support the use of the dog as a model for developing improved formulations of CGS-20625. Further investigation of the dog as a model to evaluate insoluble drug absorption is warranted.*

KEY WORDS: CGS-20625; insoluble drugs; oral absorption; bioavailability; animal model.

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INTRODUCTION

An animal model is very useful during the development of dosage forms of insoluble drugs. While *in vitro* testing may provide information about the solubility and dissolution of many compounds and is a useful screening tool, ultimately *in vivo* testing of bioavailability is necessary.

The dog can be a useful model for testing the effects of surfactants and cosolvents on the absorption of insoluble drugs or for evaluating dosage forms in general (1–3). The dog is often used for testing of oral human drugs due to the ease of sample collection, handling, and adherence to diet regimens. In addition, the dog is large enough to be dosed with solid formulations, and its gastrointestinal anatomy and physiology (pH, blood flow, microflora) are similar to man (4,5). Early clinical trials often do not investigate drug absolute bioavailability with an intravenous formulation, and humans may present drug level assay limitations.

While interspecies differences in drug metabolism and distribution and gastrointestinal factors do exist, the comparative bioavailability of solutions or dosage forms of insoluble drugs should be a function of the drug's physicochemical properties and formulation. Therefore, an animal model that reflects differences in absorption among different formulations can be invaluable when determining which formulations hold the most promise for clinical use. Furthermore, early correlation of *in vitro* dissolution data with animal results can make *in vitro* testing a more powerful screening tool for improved formulations of insoluble drugs.

The aqueous solubility of CGS-20625, a potential anxiolytic, is extremely low, 6 μg/ml, resulting in slow and erratic absorption and low bioavailability in rats. For example, absorption in rats after oral administration of 50 mg/kg in 3% cornstarch was highly variable, with a T_{max} of 2–6 hr and only 35% of the dose absorbed (unpublished results).

The solubility of insoluble drugs is often improved by the use of cosolvents, and administration of insoluble drugs as cosolvent solutions may circumvent the dissolution step, provided the drug remains in solution after dosing. In the case of CGS-20625, the solubility is improved to approximately 20 mg/ml at room temperature in neat PEG 400. Furthermore, solid dispersion formulations which offer one approach to improve absorption of insoluble drugs have been developed for CGS-20625. In this study, CGS-20625 absorption in Beagle dogs was determined after administration of 20 mg in 100% PEG 400, a solid dispersion formulation, and the powder form. In addition, drug was dosed directly into the duodenum to determine the possible benefits of an enteric coating. Results are compared retrospectively to data from two similar studies in humans and to *in vitro* dissolution data.

MATERIALS AND METHODS

Materials

PEG 400 and glycerine were purchased from Fisher (Fair Lawn, NJ). 2-aminoethanol was obtained from Sigma (St. Louis, MO) and used without further purification. CGS-20625 and related formulations were available at the Pharmaceuticals Division of Ciba-Geigy Corporation.

Animals

Beagle dogs (mean wt. 9.9 kg), obtained from Marshall Farms (North Rose, NY), were fed standard dog laboratory chow (Wayne, Bridgeton, MO), and maintained on a 12-hr light/dark cycle. Four dogs, two male and two female, were used, and all dogs were acclimated to the study procedures prior to initiation of experiments. All dogs were fasted for 16 hr prior to drug administration. All animal studies were approved by the Ciba-Geigy Animal Care Committee.

Human Subjects

Eight healthy Caucasian male volunteers ($\bar{x}$ 36.6 years, 77.3 kg) received the drug as a powder formulation. Five other healthy males ($\bar{x}$ 33.8 years, 71.6 kg) volunteered to receive PEG 400 solutions and hard gelatin capsules of CGS-20625 in a separate study. All subjects satisfied both inclusion and exclusion criteria of the clinical protocol and were required to have normal medical histories, physical examinations, and laboratory screens. Subjects fasted overnight prior to drug administration. All clinical studies were approved by Ciba-Geigy and the Institutional Review Board of the study center.

Drug Solutions and Formulations

Solutions of CGS-20625 in 100% PEG 400 were prepared at a concentration of 5 mg/ml and stirred overnight. For intravenous administration to dogs, a 10 mg/ml solution of CGS-20625 was prepared in 93.7:3.9:2.4 PEG 400:glycerine:2-aminoethanol. Any particulate matter remaining was removed by centrifugation, and the supernatant solution assayed for drug content to determine the exact dose administered. For powder administration, 20 mg of CGS-20625 was measured on an analytical balance and placed in a No. 0 white opaque capsule shell for administration to dogs. Humans were administered 20 mg of drug with 3% PVP in gelatin capsules. The solid dispersion formulation was administered orally as 2×10 mg hard gelatin capsules to dogs and humans.

Drug Administration

Animal Studies

A 2-ml bolus of CGS-20625 was administered into the cephalic or saphenous vein of conscious dogs over 40 secs. Oral administration of capsules was followed by approximately 30 ml of water to aid in swallowing. PEG solutions (4 ml) were administered to conscious dogs via oral intubation. The syringe and tube containing drug solution were weighed before and after dosing to determine the exact volume of solution delivered.

For duodenal dosing, dogs were anesthetized with an iv injection of sodium pentobarbital (25 mg/kg) and a video endoscope (Welch Allyn, Skaneateles Falls, NY) was then passsed into the stomach and advanced to the pylorus. Polyethylene tubing (ID 1.67 mm × OD 2.42 mm) was passed through the biopsy port of the endoscope and inserted 20 cm into the duodenum for delivery of the drug solution. The exact amount dosed was calculated by weight as with the stomach doses.

Clinical Studies

Hard gelatin capsules were given with 100 ml water, and powder capsules with 200 ml. PEG 400 solutions (2 ml) were administered into the stomach through an intranasal feeding tube. Duodenal intubation of human subjects was accomplished by an intranasal O'Donnell feeding tube that was allowed to pass 15 cm into the duodenum. Placement of the tube was confirmed radiographically 24 hr prior to dosing and the tube secured. The exact amount dosed into the stomach and duodenum was calculated by weight as in the dog studies.

Sample Collection

Samples (5–7 ml) were drawn from the cephalic vein into heparinized tubes at baseline (hr 0), and at 15, 30, 60, 120, 240, 360, 480, and 600 min after drug administration for oral treatments in both species, and at 2.5, 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 120, 180, 240, 360, and 480 min after the iv dose in dogs. Blood samples were centrifuged at 1000 ***g*** for 10 min and the plasma separated and frozen at −80° C until analysis.

Plasma Analysis

Samples were assayed for CGS-20625 content by HPLC using a previously published method (6). Plasma samples, 0.5 ml, were mixed with 250 ng (50 μl) internal standard (CGS-17867) and 0.5 ml of 0.1 M boric acid/KCl/NaOH buffer, pH 9.0. Samples were shaken for 10 min with 2.5 ml ethyl

acetate and the organic phase removed, dried under nitrogen, and resuspended in 200 μl mobile phase (45:40:15 methanol:water:THF). CGS-20625 was separated by a Zorbax phenyl column (5 µm, 4.6 × 150 mm, MacMod Analytical, Chadds Ford, PA) in series with a Brownlee RP-18 guard cartridge (Rainin, Woburn, MA) and detected by UV absorbance at 270 nm. Mobile phase was pumped at 1.0 ml/min, and CGS-20625 eluted at approximately 4.5 min. Standards were prepared in blank human or dog plasma over the concentration range of 10–1000 ng/ml. Quality control samples of blank dog and human plasma spiked with known amounts of CGS-20625 were prepared and assayed with every set of samples.

Dissolution Testing

Dissolution testing was performed by the paddle method defined in USP XXI for hard gelatin capsules in a Van Kel apparatus (Van Kel Industries Inc., Chatham, NJ) (7). The hard gelatin capsules were placed in 10-mesh copper helices. The distance between the paddle blade and the bottom of the vessel was maintained at 25 ± 2 mm during the test. The dissolution medium (900 ml water) was maintained at 37 ± 0.5 °C and the stirring speed at 50 rpm. Samples (1 ml) were taken without replacement at 5, 10, 15, 30, 45, 60, 75, 90, and 120 min and assayed by HPLC and/or spectrophotometry at a wavelength of 270 nm. Samples were analyzed for drug concentration immediately after collection.

Data Analysis

Pharmacokinetic analysis utilized standard methods of data treatment. Plasma level curves after intravenous administration were fitted using PCNONLIN (8). Inspection of semilogarithmic plots of intravenous drug plasma levels versus time indicated they could be described by a biexponential equation

$$C_{p(t)} = A\, e^{-\alpha t} + B\, e^{-\beta t} \tag{1}$$

where $A + B = C_p$ at time 0 (C_{po}), and α and β are the rate constants for the distribution and elimination phases, respectively. The secondary parameters A and B have been corrected for the infusion time and are reported as parameters corresponding to a bolus intravenous equation. Pharmacokinetic parameters after intravenous administration were calculated as follows:

$$AUC_{0-\infty} = \frac{A}{\alpha} + \frac{B}{\beta}$$

$$V_p = \frac{D_{iv}}{(A+B)}$$

$$t_{\frac{1}{2}}(\beta) = \frac{0.693}{\beta}$$

$$Cl = \frac{D_{iv}}{AUC_{0-\infty}}$$

where $AUC_{0-\infty}$ is the area under the curve from time zero to infinity, V_p is the volume of distribution of the central compartment, Cl is total plasma clearance, and $t_{\frac{1}{2}}(\beta)$ is beta half-life. $AUC_{0-\infty}$ after iv drug administration was also determined by the trapezoidal rule, and found to be within 5% of that calculated by model dependent methods.

All liquid stomach and duodenal dose data were normalized to a 20-mg dose. The maximum observed plasma concentration (C_{max}) and time to maximum (T_{max}) were determined, and the area under the curve (AUC) calculated using the trapezoidal rule (9). If the plasma profile exhibited more than one peak, C_{max} and T_{max} were determined from the largest peak. $AUC_{0-\infty}$ for the oral curves was determined as the area under the plasma concentration–time curve up to the last measured time point, calculated by the trapezoidal rule, plus any residual area. The residual area was calculated as the concentration at the last time point divided by the terminal rate constant. The terminal rate constant was determined by linear regression analysis of the log-linear terminal phase of the plasma concentration–time profile. Absolute bioavailability (f) of the oral doses and oral clearance (Cl_{po}) were calculated as follows:

$$f = \frac{AUC_{oral}}{AUC_{iv}}$$

$$Cl_{po} = \frac{Cl}{f} = \frac{Dose_{po}}{AUC_{po}}$$

Oral plasma level curves were analyzed by the Loo-Riegelman method using microrate constants k_{12}, k_{21}, and k_{10} obtained from nonlinear least squares regression of the intravenous data (10). The fraction of dose absorbed was normalized to absolute bioavailability.

Relative bioavailability (f_{rel}) and C_{max} ($C_{max_{rel}}$) of capsules and duodenal doses were defined as follows:

$$f_{rel(x)} = \frac{AUC_{\text{dosage form}_{(x)}}}{AUC_{\text{PEGStomachBolus}}}$$

$$C_{max_{rel(x)}} = \frac{C_{max_{\text{dosage form}_{(x)}}}}{C_{max_{\text{PEGStomachBolus}}}}$$

Statistics

All data are expressed as mean ± 1 standard error of the mean.

RESULTS

Pharmacokinetic parameters derived from intravenous plasma level curves ($n=3$) of CGS-20625 are listed in Table I. Mean plasma profiles of CGS-20625 after oral administration of 20 mg as various formulations in dogs and humans are shown in Fig. 1. Mean pharmacokinetic parameters are listed in Table II.

Plasma levels of CGS-20625 were approximately 10-fold higher and oral clearance was approximately 5-fold lower in the dog compared to man for all treatments. However, in both dog and man, absorption of CGS-20625 after administration of the powder was slow and variable, with an absolute f of 0.67 ± 0.21 in dog and f_{rel} of 0.41 in man. T_{max} was 3 hr in dog and 2 hr in man. Administration of CGS-20625 in PEG 400 solution and as the capsule reduced T_{max}, and increased C_{max} in both species. The mean C_{max} increased more than 10-fold in man from 0.009 μg/ml after CGS-20625 powder to 0.10 μg/ml after CGS-20625 in PEG 400 solution, and increased 5-fold in dogs. The $AUC_{0-\infty}$ was comparable between the solid dispersion and the PEG 400 solution in both dog (2.6 ± 0.65 vs. 2.3 ± 0.22 $\mu g \times hr/ml$, respectively), and man (0.10 ± 0.036 vs. 0.12 ± 0.043 $\mu g \times hr/ml$, respectively). In dogs, f increased to 0.84 after administration of CGS-20625 in PEG 400 solution and to 0.94 with the hard gelatin capsule, indicating almost complete absorption of the drug. Relative bioavailability of the hard gelatin capsule in man was 0.85.

No significant improvement in absorption was noted after duodenal administration in either dog or man (Fig. 1).

The fraction of drug absorbed vs. time profiles in dogs are shown in Fig. 2, the maximum fraction absorbed corresponding to the absolute

Table I. Pharmacokinetic Parameters After an Intravenous Bolus of 20 mg CGS-20625 in Dogs ($n=3$)

Parameter	$\bar{x} \pm SE$
A (μg/ml)	1.9 ± 0.65
α (hr^{-1})	29.7 ± 9.9
B (μg/ml)	1.8 ± 0.1
β (hr^{-1})	0.68 ± 0.07
$AUC_{0-\infty}$ ($\mu g \times hr/ml$)	2.7 ± 0.23
V_p (L/kg)	0.57 ± 0.11
Cl (L/hr per kg)	0.71 ± 0.11
$t_{\frac{1}{2}\beta}$ (hr^{-1})	1.1 ± 0.1

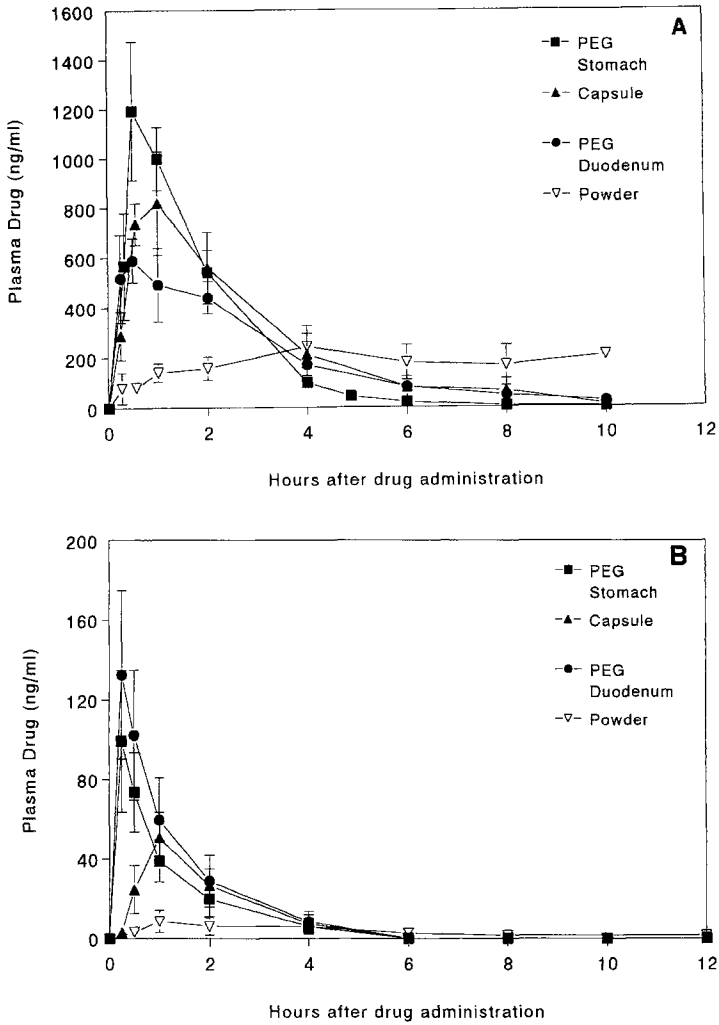

Fig. 1. Plasma concentration–time profiles of CGS-20625 in dog (A) and man (B) after oral administration of 20 mg CGS-20625 as a powder, hard gelatin capsule, and in PEG 400 solution, and after duodenal administration in PEG 400. Values represent the $\bar{x} \pm$ SE.

bioavailability of the dose. Figure 3 shows the mean plasma level profiles after oral administration of 20 mg CGS-20625 powder (A) and 2×10 mg hard gelatin capsules (B) to man and dogs together with the *in vitro* dissolution profiles of the powder and capsule formulations. Absorption of the powder appeared to be a zero-order process, with an absorption rate of 0.028 mg/min determined from the fraction absorbed curve (Fig. 2).

Table II. Pharmacokinetic Parameters After Oral Administration of 20 mg CGS-20625 to Dogs and Human Subjects

Subjects	C_{max} μg/ml	T_{max} hr	$AUC_{0-\infty}$ μg × hr/ml	Cl_{po} L/hr per kg	$C_{max_{rel}}$	f_{rel}	f
Dogs ($n=4$)							
PEG stomach							
$x \pm SE$	1.2 ± 0.12	0.5	2.3 ± 0.22	0.93 ± 0.12	—	—	0.84 ± 0.06
% CV	19		19	26			14
Capsule							
$x \pm SE$	0.89 ± 0.18	0.9	2.6 ± 0.65	0.99 ± 0.25	0.77 ± 0.19	1.1 ± 0.20	0.94 ± 0.23
% CV	36		50	50	49	37	49
Powder							
$x \pm SE$	0.26 ± 0.07	3.0	1.7 ± 0.54[a]	—[a]	0.23 ± 0.07	0.84 ± 0.29[a]	0.67 ± 0.21[a]
% CV	57		62		65	69	63
PEG duodenum							
$x \pm SE$	0.76 ± 0.12	0.6	2.0 ± 0.12	1.1 ± 0.13	0.65 ± 0.12	0.91 ± 0.11	0.75 ± 0.05
% CV	31		12	25	37	25	13
Humans ($n=5$)							
PEG stomach							
$x \pm SE$	0.10 ± 0.036	0.25	0.12 ± 0.043	4.2 ± 1.6	—	—	—
% CV	80		78	82			
Capsule							
$x \pm SE$	0.052 ± 0.014	1.0	0.10 ± 0.036	6.7 ± 3.7	0.60 ± 0.13	0.85 ± 0.18	—
% CV	62		79	123	49	47	
Powder ($n=8$)							
$x \pm SE$	0.009 ± 0.004	2.0	0.051 ± 0.021	5.1[c]	0.09 ± 0.06	0.41 ± 0.25[d]	—
% CV	172		168		172	168	
PEG duodenum							
$x \pm SE$	0.13 ± 0.042	0.25	0.18 ± 0.067	3.9 ± 1.8	2.8 ± 0.60	1.3 ± 0.22	—
% CV	70		85	104	47	33	

[a] Due to slow absorption, it was not possible to determine $AUC_{0-\infty}$. $AUC_{0-10\,hr}$ was used for these calculations.
[b] Intravenous data not obtained.
[c] Calculation based on mean $AUC_{0-\infty}$ since 5 of 8 subjects had $AUC_{0-\infty}=0$.
[d] Calculation based on mean PEG stomach $AUC_{0-\infty}$.

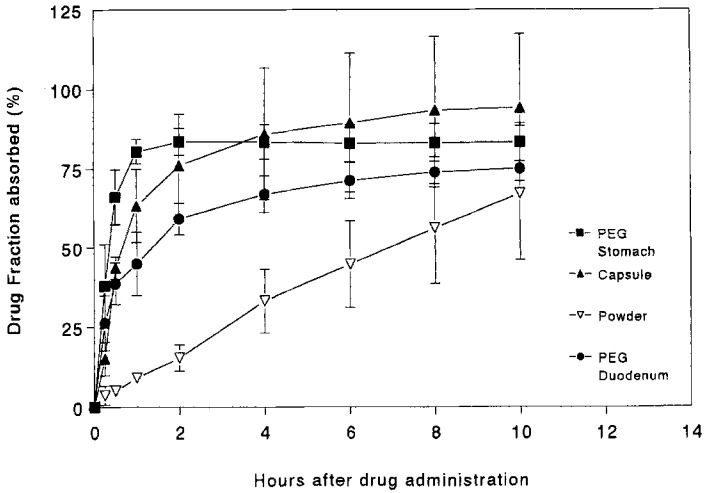

Fig. 2. Fraction of drug absorbed–time profiles in dogs after administration of 20 mg CGS-20625 orally as a powder, hard gelatin capsule, and PEG 400 solution, and duodenally as a PEG 400 solution. The fraction of drug absorbed was normalized to absolute bioavailability. Values represent the $\bar{x} \pm SE$.

Absorption of CGS-20625 from the dosage form did not appear to be either a zero- or a first-order process. However, the initial absorption rate for the dosage form, calculated over the first hour, was 0.22 mg/min. The initial *in vitro* dissolution rates for 20 mg CGS-20625 powder and dosage form were 0.16 and 2.8%/min, respectively.

DISCUSSION

The relative rates of CGS-20625 absorption among different dosing groups were similar between man and dog. In both man and dog, the absorption rate after oral dosing was in the order of powder < capsule < PEG 400 stomach. Similarities between the species are also illustrated by comparing the pharmacokinetic parameters of the capsule and powder (see Table II). In both species, C_{max} and f relative to the PEG 400 stomach dose were higher after administration of the caspsule than the powder. However, there was a greater effect of formulation on relative C_{max} than f in both species, suggesting that the different formulations have more effect on the *rate* rather than on the extent of drug absorption. These comparisons demonstrate the utility of the dog model for the evaluation of CGS-20625 formulations.

Due to the retrospective nature of the studies in humans, the volume of coadministered fluid varied, as the powder was administered with 200 ml

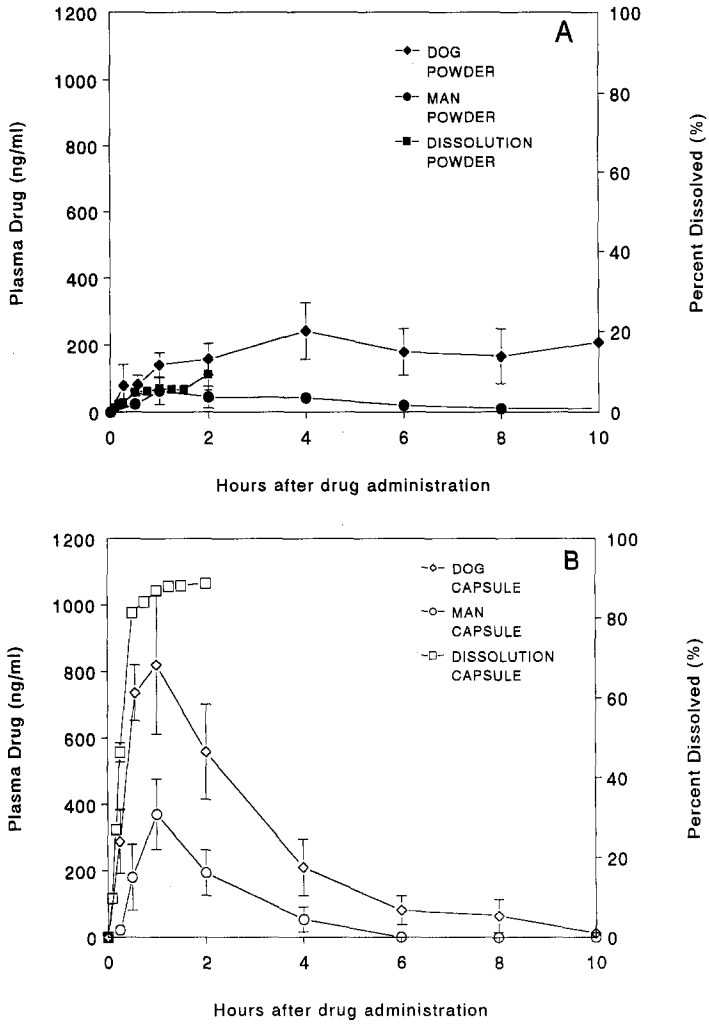

Fig. 3. Plasma concentration–time profiles of CGS-20625 in dog and man after oral administration of 20 mg powder (A) and 2×10 mg hard gelatin capsules (B) plotted with *in vitro* dissolution profiles of the powder (A) and hard gelatin capsules (B). Values represent the $\bar{x} \pm SE$.

of water, and the capsule with 100 ml. Despite the differences in coadministered fluid volume, the relative rate of absorption was capsule > powder, similar to the dog.

Plasma levels of CGS-20625 were approximately 10-fold higher in the dog than in man. In addition, oral clearance in man was approximately 5-fold greater than in the dog. There was a greater degree of variability in the

human data compared to the dog. This could be due to a higher plasma clearance and/or a lower bioavailability of CGS-20625 in man compared to dog. Differences in first-pass metabolism of CGS-20625 in man compared to the dog may explain these results. The low coefficients of variation within the dog groups and the high bioavailability of the drug suggest a minimal first-pass metabolism of this drug in the dog. Greater first-pass metabolism in man would not only account for lower drug plasma levels and higher oral clearance but also may contribute to the high degree of variability found in man compared to dog (Table II). Furthermore, in the case of a drug with significant first-pass metabolism, the consequence of a lower rate of absorption is that a greater fraction of the drug is metabolized on first pass through the liver. Since the rate of absorption is in the order of PEG 400 stomach > powder, this may explain the lower relative bioavailability of the powder in man compared to dog. However, the metabolism of CGS-20625 has not yet been elucidated.

The relative bioavailability of the duodenal dose of CGS-20625 in dog was 30% less than that in man (Table II). Reasons for this species difference are not clear. Differences observed between man and dog may be attributed to pH differences between the small intestine of dog and man. The solubility and the rate of dissolution of CGS-20625 are greater in simulated gastric fluid (SGF) than in simulated intestinal fluid (SIF) (solubility is 0.52 mg/ml in SFG and 0.025 mg/ml in SIF). Since the small intestinal pH of the dog is approximately one unit higher than in man (5), a drop in the solubility of CGS-20625 may account for its lower relative bioavailability after duodenal dosing in the dog as compared to man. However, solubility and dissolution rates have not been determined over the pH range of 5–8. Therefore, the effect of pH in this range of the absorption of CGS-20625 is unknown. The effect of anesthesia was ruled out after gastric administration of CGS-20625 in PEG 400 to anesthetized dogs resulted in bioavailability comparable to that in conscious dogs (unpublished results).

The relationship between CGS-20625 solubility, dissolution, and absorption is further demonstrated by comparing oral absorption and dissolution data. Based on initial *in vitro* dissolution rates for 20 mg CGS-20625, the capsule dissolved 17 times faster than the powder. The initial *in vivo* absorption rate of the CGS-20625 hard gelatin capsule was 8 times greater than the powder, demonstrating that relative *in vitro* dissolution differences were reflected *in vivo*. In the case of the powder, dissolution is clearly the rate-limiting step for absorption (Fig. 3). The ability to predict relative rates of *in vivo* absorption in an animal model and in man based on *in vitro* dissolution rates is important, particularly for insoluble drugs. These data demonstrate an excellent correlation between *in vivo* absorption and *in vitro* dissolution.

In summary, absorption of CGS-20625 from powder was slow and erratic in dogs and man due to poor dissolution. PEG 400 improves drug solubility and consequently absorption in dog and man. The correlation in the relative rates of absorption of dosage forms between man and dog suggests that this animal model may be valuable for the evaluation of improved dosage forms of CGS-20625. However, the correlation between man and dog may be due to the large variability in the human data and therefore, any species differences may not be discernible. Furthermore, the dog is conducive to the evaluation of CGS-20625 oral formulations due to the low first-pass metabolism. In a model designed to measure the effects of formulations on drug absorption, high levels of metabolism would confound interpretation of pharmacokinetic data. In particular, results in dogs demonstrate that the solid dispersion formulation provided for complete oral bioavailability. Definitive metabolism studies would allow for differentiation between formulation and physiological effects on dosage form performance in man.

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