β-Cyclodextrin Derivatives, SBE4–β-CD and HP–β-CD, Increase the Oral Bioavailability of Cinnarizine in Beagle Dogs

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Abstract □ The absolute bioavailabilities (F_{abs}) of cinnarizine after oral administration as two modified β-cyclodextrin (SBE4–β-CD or HP–β-CD) solutions, an aqueous suspension, and two capsules in fasted beagle dogs were determined. Cinnarizine was administered orally (25.0 mg) and intravenously (12.5 mg) to four dogs. Blood samples were drawn for 24.5 h postdosing, and cinnarizine levels in plasma were determined by HPLC with spectrofluorometric detection. Cinnarizine pharmacokinetics after iv administration as a 1.25 mg/mL SBE4–β-CD solution followed triexponential behavior ($t_{1/2}$ = 12.6 ± 0.4 h and Cl = 1.4 ± 0.17 L/h/kg). A very low bioavailability of cinnarizine with a wide interanimal variation was observed after oral administration as a suspension (F_{abs} = 8 ± 4%) or capsule containing only cinnarizine (F_{abs} = 0.8 ± 0.4%). Administration of cinnarizine as a CD complex either as a solution (F_{abs} = 55–60%) or in a capsule (F_{abs} = 38 ± 12%) significantly enhanced the bioavailability. Since the solutions showed excellent bioavailability, the logical conclusion is that, once presented as a solution, cinnarizine is well absorbed and that cinnarizine rapidly dissociates from its inclusion complexes. Presumably, the elevated bioavailability from the SBE4–β-CD containing capsule was due to rapid dissolution and release of cinnarizine.

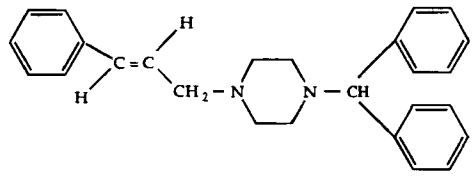
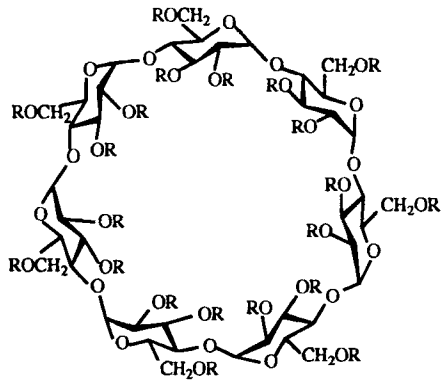


Figure 1—The chemical structure of cinnarizine.



R = -$CH_2CH_2CH_2CH_2SO_3Na$ or -H
SBE4-β-CD
(average degree of sulfobutyl substitution is four)

Figure 2—The chemical structure of SBE4–β-CD.

Introduction

Cinnarizine (Figure 1), a piperazine derivative, is clinically used as a vasodilator, antihistaminic, and antiallergic agent.[1,2] It is a weak base (pK_{a1} 1.95[3], and pK_{a2} 7.47[4]) exhibiting pH-dependent dissolution behavior; while it dissolves readily at pH 1 (≈1.5 mg/mL), it has a very low solubility and therefore low dissolution at pH values greater than 4.5.[5] Therefore, as expected, the bioavailability of cinnarizine from oral tablets is largely determined by the amount dissolved in the stomach since absorption of orally administered cinnarizine is significantly higher in humans[5] and dogs[6,7] with high gastric acidity than those with low gastric acidity. Consequently, administration of cinnarizine as a tablet or capsule may not result in therapeutical levels of cinnarizine in patients with low gastric acidity.

Few methods have been developed to enhance the bioavailability of orally administered cinnarizine and compounds with similar dissolution properties. Cinnarizine bioavailability in beagle dogs from a lipid vehicle (oleic acid) was greater than that of a conventional tablet.[8] Unmodified cyclodextrins (CDs) have also been used as adjuvants in an attempt to increase cinnarizine bioavailability.[9] CDs are a group of homologous cyclic oligosaccharides consisting six, seven, or eight glucose units, α-, β-, or γ-cyclodextrin, respectively. Inclusion complex formation between a drug and a cyclodextrin have been used to improve drug solubility and/or stability[10,11] as well as bioavailability.[12,13] The *in vitro* dissolution rate of cinnarizine as a cinnarizine/β-CD complex was about 30 times larger than that of cinnarizine at pH 5.0.[14] However, the bioavailability of cinnarizine from a β-CD-containing tablet was not significantly increased over a control tablet[9] unless D,L-phenylalanine was simultaneously administered.[15,16]

Modified β-CD derivatives, such as 2-hydroxypropyl-CD (HP–β-CD) and SBE–β-CDs (variably substituted sulfobutyl ether derivatives of β-cyclodextrin),[17] have been developed with the purpose of improving the toxicity, aqueous solubility, and subsequent pharmaceutical usefulness of β-CD. In SBE–β-CDs, an anionic sulfonate group is spaced from the cyclodextrin cavity by a butyl chain (Figure 2). The drug solubility enhancements observed with SBE–β-CDs, such as SBE4–β-CD (an SBE–β-CD derivative with an average degree of substitution of four) used in this study, are comparable or higher than those observed for HP–β-CD.[18,19]

To our knowledge, the bioavailability of cinnarizine after oral administration as a solution has not been studied and only one iv pharmacokinetic report is available.[6] In that study, cinnarizine was administered intravenously as a polyethylene glycol 400 solution in beagle dogs. In the present study, cinnarizine solutions were prepared in the presence of 0.075 M SBE4–β-CD and HP–β-CD at pH 4.5. Absolute bioavailabilities of cinnarizine in beagle dogs after oral administration as solutions, a suspension, and as two capsules were compared.

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Experimental Section

Chemicals—The synthesis and identification procedures for SBE4–β-CD (mw 1798.6–1933.7) have been described previously.[17,20] HP–β-CD (Encapsin; mw 1338; degree of molar substitution, 0.6) was a gift from American Maize-Products Co. (Hammond, IN). Cinnarizine (mw 368.5), meclizine, and sodium phosphate were purchased from Sigma Chemical Co. (St. Louis, MO). Acetonitrile (HPLC-grade), carbon tetrachloride, and ammonium dihydrogen phosphate were purchased from Fisher Scientific Co. (Fair Lawn, NJ).

Phase-Solubility Studies—The stability constants (K_c) for inclusion complex formation between cinnarizine and SBE4–β-CD or HP–β-CD were determined using the phase solubility method.[21] Excess cinnarizine was added to phosphate buffer solutions (0.16 M, ionic strength of 0.5, pH 4.5) containing various concentrations (0–25 mM) of SBE4–β-CD or HP–β-CD, and the suspensions were agitated at 25 °C for 72 h. The pH of the suspensions was monitored during the equilibration. The pH of the suspensions was adjusted to 4.5 with HCl if necessary. After equilibration, the solutions were centrifuged, and the clear supernatant was diluted with HPLC mobile phase and analyzed by the reversed-phase HPLC method as described in the analytical section. The K_c (1:1) for the cinnarizine/SBE4–β-CD and cinnarizine/HP–β-CD complexes at pH 4.5 were calculated from the equation K_c (1:1) = slope/[S_o(1 − slope)], where slope is the slope of the phase-solubility diagrams and S_o is the determined solubility of cinnarizine in phosphate buffer (pH 4.5) in the absence of SBE4–β-CD or HP–β-CD.

Preparation of Dosage Forms—Cinnarizine for iv solution and oral administration was prepared in 10 mM phosphate buffer solution at pH 4.5 (1.25 mg/mL for the iv injection and 2.5 mg/mL for the oral solution) in the presence of SBE4–β-CD (37.5 mM for the iv injection and 75.0 mM for oral) or HP–β-CD (75 mM). SBE4–β-CD or HP–β-CD was first dissolved in 10 mL of phosphate buffer solution and the pH of solutions was then adjusted to about 3 with HCl before mixing with cinnarizine. The mixture was then ultrasonicated for a few hours and stirred with TeflonR-coated magnet bars overnight. The final pH of solution was adjusted to 4.5 with NaOH. Cinnarizine suspension (2.5 mg/mL, 10.0 mL) was identical (10 mM phosphate buffer solution at pH 4.5) to the solutions minus the CDs. For the iv injection, the solution was made isotonic by the addition of sodium chloride and was filtered through a 0.2 μm nylon-membrane filter (Gelman Sciences, Ann Arbor, MI) just prior to administration. The cinnarizine capsule consisted of just cinnarizine (25 mg) in a hard gelatin capsule (No. 4, Eli Lilly and Co., Indianapolis, IN). To prepare a solid cinnarizine/SBE4–β-CD powder, with a molar ratio of cinnarizine to SBE4–β-CD of 1:4.6, a cinnarizine solution (2.5 mg/mL) in the presence of SBE4–β-CD (30 mM) was first prepared as described above (in 10 mM phosphate buffer at pH 4.5). The solution was then lyophilized (The Virtis Co., Cardiner, NY) and the resulting solid powder, containing 25.0 mg of cinnarizine, was placed into two hard gelatin capsules (No. 00, Eli Lilly and Co., Indianapolis, IN).

Absorption study—The experimental animals used in this study were four adult male beagle dogs (11.9–16.5 kg). The dogs had a regular diet between the experiments.

Prior to cinnarizine administration the dogs were fasted overnight (18–20 h). During the studies, water was allowed *ad libitum* and solid meals were given at 8 h postdosing. The intravenous bolus dose of cinnarizine (10 mL, 12.5 mg) was administered via the cephalic vein. Cinnarizine solutions and suspension (10 mL, 25.0 mg) were given orally via a gastric tube followed immediately by 10 mL of water. Gelatin capsules containing 25.0 mg of cinnarizine were administered to the dogs orally followed by about 5 mL of water.

The administration of the cinnarizine involved essentially two studies. In the first, the iv bolus, two oral solutions, and one oral suspension were administered in a randomized 4 × 4 crossover design with at least a 2 week wash-out period between doses. After completing this study, the two capsule formulations were given to the same dogs.

Blood samples (3 mL) for cinnarizine analysis were taken from cephalic, saphenous, or jugular vein just prior to (blank plasma) and 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, and 24.5 h after oral administration, and 2, 6, 10, 20, and 40 min and 1, 2, 4, 6, 8, and 24.5 h after iv bolus administration. The blood samples were centrifuged for 5 min (Micro-Centrifuge, Model 235 C, Fisher-Scientific), plasma removed and stored at −20 °C until assayed as described below.

Analytical Procedure—Cinnarizine concentration in the plasma was assayed by a modified HPLC method with spectrofluorometric detection.[6,8,22] To 1.0 mL of plasma was added 150 μL of 0.5 M HCl, 100 μL of internal standard solution (meclizine; 200–300 μg/mL in acetonitrile–H_2O (70:30)), and 100 μL of acetonitrile–H_2O (70:30). The mixture was throughly mixed, 1.0 mL of carbon tetrachloride was added, and the mixture was vortexed for 30 s. After centrifugation, the organic layer was removed and evaporated to dryness under a stream of nitrogen. The residue was dissolved in 400 μL of acetonitrile–H_2O (70:30) and 50 μL was injected into an HPLC. The results were calculated from peak-area ratios.

The HPLC system consisted of a Beckman 110B pump (Berkley, CA), a Rheodyne 7125 injector, a Hypersil ODS column (15 cm x 4.6 mm i.d., 5 μm), a Shimadzu RF-535 fluoroscence detector (Kyoto, Japan) and a Shimadzu CR-601 integrator (Kyoto, Japan). The HPLC conditions were as follows: injection volume, 50 μL; flow rate, 1.7 mL/min; excitation wavelength, 260 nm; emission wavelength, 315 nm. The mobile phase consisted of acetonitrile and 10 mM ammonium dihydrogen phosphate (70:30). Under these conditions, the retention times for cinnarizine and meclizine (internal standard) were 10.5 and 13.5 min, respectively.

Individual standard curves were prepared for each dog by spiking each dog's blank plasma with known amounts of cinnarizine in order to achieve concentrations ranging from 5.5 to 545 ng/mL (six points). Standard curves were linear ($r^2 \geq 0.998$), which made one-point calibration feasible. The standards (three different concentrations; one near the lowest sample concentration, one near the center, and one near the highest sample concentration) were prepared daily in blank plasma and were used to calculate cinnarizine concentration in samples. The lower limit of quantitation of cinnarizine was 2 ng/mL in plasma.

The intraday precision of the method (coefficient of variation) was assessed by extracting and analyzing cinnarizine plasma samples at three different concentrations six times in one day. The intraday precision was 3.6% (5.1 ng/mL, $n = 6$), 2.4% (115.5 ng/mL, $n = 6$), and 1.9% (306.5 ng/mL, $n = 6$). The interday precision (coefficient of variation) was determined by extracting and analyzing cinnarizine plasma samples at three different concentrations on five consecutive days. The interday precision was 7.1% (5.0 ng/mL, $n = 5$), 4.3% (67.9 ng/mL, $n = 5$), and 1.4% (199.6 ng/mL, $n = 5$).

The recovery of cinnarizine from plasma was determined at two different concentrations ($n = 4$) by comparison of the absolute peak areas from the extracted samples to the areas obtained from unextracted standard solutions prepared in mobile phase. The recoveries (mean ± SE) at concentrations 15.5 and 102 ng/mL were 99.1 ± 1.1% and 91.2 ± 1.0%, respectively.

Data Analysis—Pharmacokinetic analysis utilized standard methods of data treatment. Inspection of semilogarithmic plots of the postinjection cinnarizine plasma levels-versus-time curves indicated that they could not be described by a biexponential equation. This conclusion was confirmed by the results that were obtained with the SigmaPlot 4.14 curve-fitting program (Macintosh); when the unweighted iv data was fitted to the biexponential equation, the results were unsatisfactory but the triexponential equation gave satisfactory results. Cinnarizine concentration in plasma (C) after an intravenous bolus was best described by the triexponential equation: $C = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t} + A_3^{-\lambda_3 t}$, where t is the time. Plasma terminal half-life ($t_{1/2}$) is given by $t_{1/2} = 0.693/\lambda_3$. Areas under the concentration versus time curves from 0 to infinity ($AUC_{0-\infty}$) following the iv injection were estimated by using the equation $AUC_{0-\infty} = A_1/\lambda_1 + A_2/\lambda_2 + A_3/\lambda_3$.[23] For oral dosage forms, $AUC_{0-\infty}$ was calculated in two steps: $AUC_{0-24.5h}$ was calculated by using the linear trapezoidal method and to this partial area was added $AUC_{24.5h-\infty}$ that was estimated by dividing cinnarizine concentration at 24.5 h post-dosing by λ_3.[23] Clearance values (Cl) were calculated from $Cl = D_{iv}/AUC_{0-\infty}$, where D_{iv} is the intravenous dose. Mean residence times (MRT) were calculated from $MRT = AUMC_{0-\infty}/AUC_{0-\infty}$, where AUMC is the area under the (time × cinnarizine concentration) versus time curve.[23] The apparent volume of distribution at steady state (V_{ss}) is given by Cl × MRT. Peak cinnarizine concentration in plasma (C_{max}) and t_{max} were calculated from the actual data points. The fraction of an oral dose that was absorbed into the systemic circulation (F_{abs}) was calculated as follows $F_{abs} = (D_{iv}AUC_{0-\infty,oral})/(D_{oral}AUC_{0-\infty,iv})$.[23]

A one-factor analysis of variance (ANOVA for repeated measurements) was used to test the statistical significance of differences between groups; significance in the differences in the means was

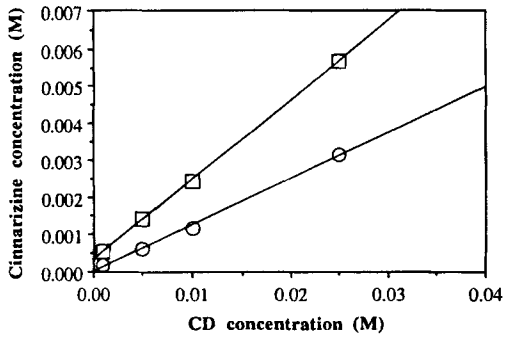

Figure 3—Phase-solubility diagrams for cinnarizine in the presence SBE4–β-CD (□) and HP–β-CD (○) (0.16 M phosphate buffer, pH 4.5) at 25 °C.

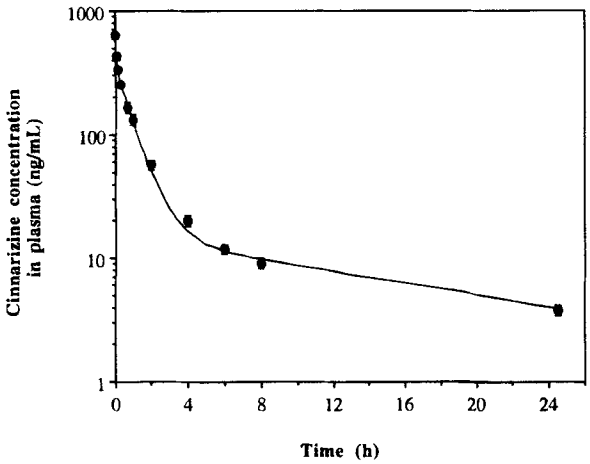

Figure 4—Cinnarizine plasma concentration in dogs (mean ± SE, $n = 4$) after intravenous administration of 12.5 mg of cinnarizine (●) and theoretical curve (solid line) obtained by fitting the observed data to the triexponential equation $C = 485.2e^{-14.1t} + 329.0e^{-1.068t} + 15.1e^{-0.0558t}$, where t is the time (h).

tested using Fisher's protected least significant difference (PLSD) at 95% confidence.

Results

Phase Solubility Study—Figure 3 shows the phase-solubility diagrams of cinnarizine with SBE4–β-CD or HP–β-CD in phosphate buffer solution (0.16 M, ionic strength of 0.5, pH 4.5) at 25 °C. The high buffer concentration and ionic strength used here, versus the conditions for the formulations, were due to an attempt to maintain a constant pH. For the solution formulations, the final pH was adjusted. The phase solubility diagrams are AL-type,[21] indicating formation of a 1:1 cinnarizine/SBE4–β-CD complex at this pH and cyclodextrin concentration range. K_c values for the cinnarizine/HP–β-CD and cinnarizine/SBE4–β-CD complexes were determined to be 2242 and 4276 M^{-1}, respectively. The intrinsic solubility (S_o) of cinnarizine in pH 4.5 phosphate buffer solution at 25 °C was 23.3 μg/mL (0.063 mM).

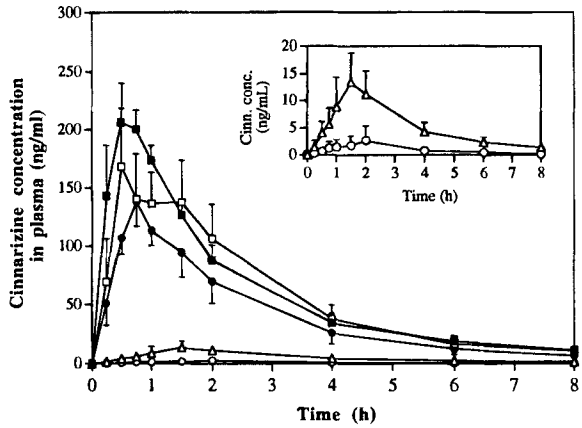

Figure 5—Cinnarizine plasma concentration in dogs (mean ± SE, $n = 4$) after oral administration of 25 mg cinnarizine: (■) HP–β-CD solution; (□) SBE4–β-CD solution; (●) capsule containing solid cinnarizine/SBE4–β-CD complex; (C) cinnarizine aqueous suspension, pH 4.5; (○) capsule containing cinnarizine but no SBE4–β-CD.

Pharmacokinetic and Bioavailability Study—All the dosage forms were well-tolerated by the beagle dogs, i.e. no obvious side effects were observed from the drug or vehicles. The semilog plot of mean plasma concentration (ng/mL) versus time (h) after a single intravenous bolus dose is shown in Figure 4. The mean cinnarizine concentration in plasma (C) after an intravenous bolus (10 mL of 10 mM phosphate buffer (pH 4.5) containing 12.5 mg of cinnarizine and 37.5 mM of SBE4–β-CD) was best described by the triexponential equation: $C = 485.2e^{-04.1t} + 329.0e^{-1.068t} + 15.1e^{-0.0558t}$, where t is the time (h). The mean values (±SE) of $t_{1/2}$, $AUC_{0-\infty}$, Cl, MRT, and V_{ss} for intravenously administered cinnarizine were 12.6 ± 0.4 h, 623.8 ± 38.3 ng h/mL, 1.4 ± 0.17 L/h/kg, 8.0 ± 1.0 h, and 11.7 ± 2.8 L/kg, respectively.

The mean values of pharmacokinetic parameters for all the oral dosage forms (dose of cinnarizine, 25.0 mg) are summarized in Table 1. The mean plasma concentration versus time profiles of cinnarizine following oral administration as a suspension, solutions or capsules are shown in Figure 5. The mean C_{max} and F_{abs} values (±SE) of orally administered cinnarizine decreased in the order cinnarizine/SBE4–β-CD-

Table 1. Mean Values of Pharmacokinetic Parameters for Cinnarizine (CN) in Plasma after Oral Administration (25.0 mg) in Various Dosage Forms to Beagle Dogs

Treatment	Mean Values ± SEM ($n = 4$)			
	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng h/mL)	F_{abs}	t_{max} (h)
Solutions				
CN + 75 mM SBE4–β-CD	220.7 ± 17.0[b–d]	729.5 ± 135.4[b–d]	0.60 ± 0.13[b–d]	0.75 ± 0.25
CN + 75 mM HP–β-CD	216.7 ± 24.4[b–d]	665.0 ± 108.9[b–d]	0.55 ± 0.11[b–d]	0.56 ± 0.06[c]
Capsule				
CN + SBE4–β-CD	145.7 ± 20.6[c,d]	457.3 ± 125.4[c,d]	0.38 ± 0.12[c,d]	0.88 ± 0.22
Suspension				
CN in buffer	17.7 ± 5.4	93.6 ± 47.9	0.08 ± 0.04	1.30 ± 0.3
Capsule				
CN, no SBE4–β-CD	3.3 ± 1.1[a]	9.9 ± 5.0[a]	0.008 ± 0.004[a]	ND[a,e]

[a] Concentration of CN in plasma of dog 3 was less than the lower quantitation limit (i.e. 2 ng/mL) in all samples. C_{max}, $AUC_{0-\infty}$, and F_{abs} values for dog 3 were assumed to be equal to 0 when mean values were calculated. [b] Significantly different from the value for the capsule containing CN and SBE4–β-CD. [c] Significantly different from the value for the suspension. [d] Significantly different from the value for capsule containing CN but no SBE4–β-CD ($p < 0.05$ by ANOVA, Fisher's PLSD test). [e] Not determined.

solution (220.7 ± 17.0 ng/mL, 60 ± 13%) ≈ cinnarizine/HP-β-CD-solution (216.7 ± 24.4 ng/mL, 55 ± 11%) > capsule containing SBE4-β-CD (145.7 ± 20.6 ng/mL, 38.0 ± 12%) > suspension (17.7 ± 5.4 ng/mL, 8 ± 4%) > capsule in the absence of SBE4-β-CD (3.3 ± 1.1 ng/mL, 0.8 ± 0.4%) (Table 1). For the oral capsule without SBE4-β-CD, one dog had no detectable cinnarizine plasma levels (<2 ng/mL). t_{max} values qualitatively followed the order of bioavailability, i.e. t_{max} increased as F_{abs} decreased.

Considerable interindividual variability in C_{max} and F_{abs} values was seen after oral administration of cinnarizine as a suspension or capsule in the absence of the CDs (Table 1). For example, C_{max} values ranged from 7.1 to 28.5 ng/mL while F_{abs} values ranged from 0.008 to 0.13 after administration of cinnarizine suspension. A smaller variation in the pharmacokinetic parameters was seen after administration of the SBE4-β-CD-containing capsule or the two solutions.

Discussion

Previous pharmacokinetic/bioavailability studies with cinnarizine in beagle dogs have followed the cinnarizine concentration for 8 h.[6-8] In the present study, the pharmacokinetics of various oral or intravenous doses seemed better described when the blood sampling period was extended up to 24.5 h postdosing. Because of the longer sampling time, cinnarizine was observed to exhibit a mean terminal half-life of about 12-13 h compared to about 5 h observed earlier in beagle dogs.[6] Similar oral dose studies in humans where the blood sampling period was 12 h or less suggested an apparent terminal half-life of 3-5 h.[24-26] However, a recent human study wherein the blood sampling period was extended to 72 h showed a mean terminal half-life of about 24 h and that cinnarizine pharmacokinetics after a single oral dose via tablet could not be described by a one-compartment model.[27]

An intravenous bolus dose of cinnarizine at 1 mg/kg is well-tolerated by beagle dogs.[6] For this reason, a similar iv dose was administered in the present study. Since it was known that the disposition of cinnarizine in beagle dogs can be regarded as a linear function of dose at doses up to 25 mg,[7] the bioavailability of cinnarizine in the present study was performed at 25 mg, and for assessing F_{abs}, the AUCs were corrected for dose differences.

A very low bioavailability of cinnarizine with a wide interanimal variation was observed after oral administration either as the suspension or the capsule containing just cinnarizine. In a previous study, mean C_{max} levels were between 50 and 70 ng/mL after oral administration of 25 mg of cinnarizine as capsules (commercially available in Japan) in the absence of any CD in beagle dogs.[7] However, interanimal variation in C_{max} values was wide, ranging from less than 5 to 160 ng/mL. It has been reported in numerous other studies that there is a considerable interindividual variability in cinnarizine plasma levels after its oral administration in dogs and humans.[5,6,25] Differences in gastric acidity, and thus in the amount of cinnarizine dissolved in the stomach, among subjects have been suggested as the most logical explanation for the variability in oral cinnarizine bioavailability. Our results support this hypothesis since a smaller interanimal variation was seen after administration of cinnarizine as the two solutions and after iv administration than after oral administration as a suspension or capsules. Compared to the suspension and capsule containing just cinnarizine, the capsules containing SBE4-β-CD showed a significantly increased bioavailability of cinnarizine in each dog and decreased the interanimal variation. The bioavailabilities of cinnarizine from the two CD solutions were not significantly different from each other and both were superior to the suspension and capsule containing just cinnarizine as well as the capsule containing cinnarizine and SBE4-β-CD.

Cl and V_{ss} values of cinnarizine shown in this study are in good agreement with a previous study (Cl = 1.6 L/h/kg and V_{ss} = 8.75 L/kg).[6] Cinnarizine undergoes extensive metabolism in humans.[2] Assuming that cinnarizine is also extensively metabolized in dogs and that elimination occurs primarily by hepatic metabolism, the hepatic extraction ratio (ER) can be estimated by assuming that total clearance is equal to liver clearance. Assuming a hepatic blood flow in dogs of 2.4 L/h/kg,[28] a hepatic ER value of 0.58 can be estimated. Even if this value is an overestimate of the true ER value, this calculation suggested that cinnarizine could be subject to up to 50-60% presystemic metabolism. Therefore, the F_{abs} of 55-60% seen with the CD solutions of cinnarizine may in fact indicate complete absorption of the oral cinnarizine.

The increased aqueous solubility of cinnarizine at pH 4.5 in the presence of SBE4-β-CD and HP-β-CD indicated that both SBE4-β-CD and HP-β-CD are able to form inclusion complexes with cinnarizine. The solubility enhancements observed for SBE4-β-CD were higher than those observed for HP-β-CD, and thus, less SBE4-β-CD than HP-β-CD could be used for formulating cinnarizine solutions. An earlier study proposed that β-CD-containing cinnarizine tablets do not show increased bioavailability because cinnarizine is not released from the cinnarizine/β-CD complex without simultaneous administration of a competing agent.[16] An alternative explanation might be the relatively low solubility of the cinnarizine/β-CD complex (forms a B-type phase solubility diagram) or the fact that the β-CD was not present in excess. Dissolution of the cinnarizine/β-CD complex, without excess β-CD, may have resulted in cinnarizine precipitation. It is generally assumed that a drug must be released from the drug/CD complex before drug absorption since drug/β-CD complexes do not penetrate through the biological membranes largely due to the hydrophilic character of the CDs.[29,30] In the present study, cinnarizine was readily released from the inclusion complexes with SBE4-β-CD or HP-β-CD without simultaneous administration of any competing agent since bioavailability of cinnarizine was increased and t_{max} values did tend to decrease when cinnarizine was administered as a cinnarizine/SBE4-β-CD or cinnarizine/HP-β-CD complex.

In conclusion, the oral bioavailability of cinnarizine was significantly increased and interanimal variation was decreased substantially in beagle dogs when cinnarizine was administered as either cinnarizine/SBE4-β-CD or cinnarizine/HP-β-CD solutions or as a SBE4-β-CD containing capsule when compared to cinnarizine in the absence of the CDs. If the safety of these modified cyclodextrins can be established, they appear to be useful additives, or enabling agents, for the formulation of sparingly water soluble drugs, including weakly basic amines such as cinnarizine.

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