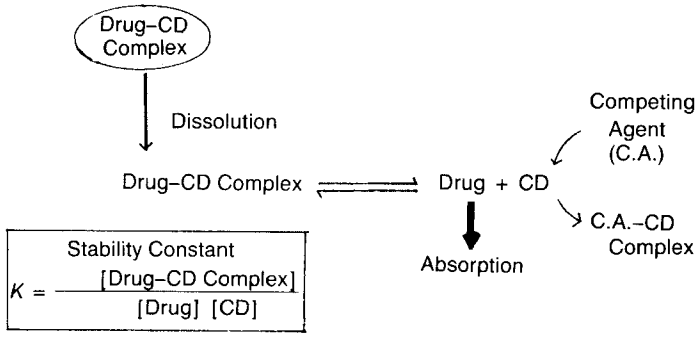
Enhancement of Bioavailability of Cinnarizine from Its β-Cyclodextrin Complex on Oral Administration with DL-Phenylalanine as a Competing Agent

To the Editor:

Inclusion complex formation of a drug with cyclodextrin (CD) is known to bring about enhancement of solubility,[1,2] dissolution rate,[3,4] and bioavailability[5-8] of the drug. The enhancement of bioavailability thereby reported is generally based on an increase in solubility and dissolution rate of the drug due to CD complex formation. However, the drug absorption rate of the complex through membranes may decrease since only free drug is absorbed. Therefore, if the stability constant is large, CD complex formation is not as effective in the enhancement of bioavailability.

This communication is concerned with an improvement of the bioavailability of a drug by administering its CD complex together with another compound, which competes with the β-CD molecule in complex formation in aqueous solution (competing agent). Scheme I explains the process of drug absorption



Scheme I

from the CD complex and the role of a competing agent. After both the complex and the competing agent dissolve, the concentration of free drug that is available for absorption may increase.

The present examination was done using cinnarizine (CN) and β-CD as a drug–CD complex and DL-phenylalanine as a competing agent. It has been reported that L-phenylalanine forms an inclusion complex with β-CD,[9] and thus, DL-phenylalanine was expected to form an inclusion complex with β-CD.

The CN/β-CD complex (molar ratio, 1:2) was prepared by the method described in a previous paper.[10] Two tablets of CN and CN/β-CD complex, containing 25 mg (6.78×10^{-5} M) of CN in each tablet, were administered alone or together with 2 g (1.21×10^{-2} M) of DL-phenylalanine, in four gelatin capsules, with 30 mL of water to three male beagle dogs fasted for 24 h. This was the experimentally possible maximum dose, as the minimum effective amount of the competing agent was not known.

At given intervals, 2.5-mL blood samples were taken, and the plasma concentration of CN was determined as follows. One milliliter of plasma sample, 0.5 mL of 1 M HCl, and 5 mL of ether were added to a glass-stoppered centrifuge tube, shaken well, and centrifuged. After the organic layer was discarded, the aqueous layer was extracted with 5 mL of dichloromethane, and the dichloromethane phase was evaporated to dryness. The residue was dissolved in 100 μL of mobile phase [acetonitrile:0.01 M $NH_4H_2PO_4$ (70:30)] containing 100 μg of meclizine hydrochloride as an internal standard, and 50 μL of the solution was injected into a Shimadzu LC-5A HPLC. The eluant was monitored spectrofluorometrically by using a fluorescence monitor (Shimadzu RF-530). The excitation and emission wavelengths were 260 and 315 nm, respectively. A column of Nucleosil C_{18} (5-μm particle size, 4 mm × 25 cm) was used for the analysis.

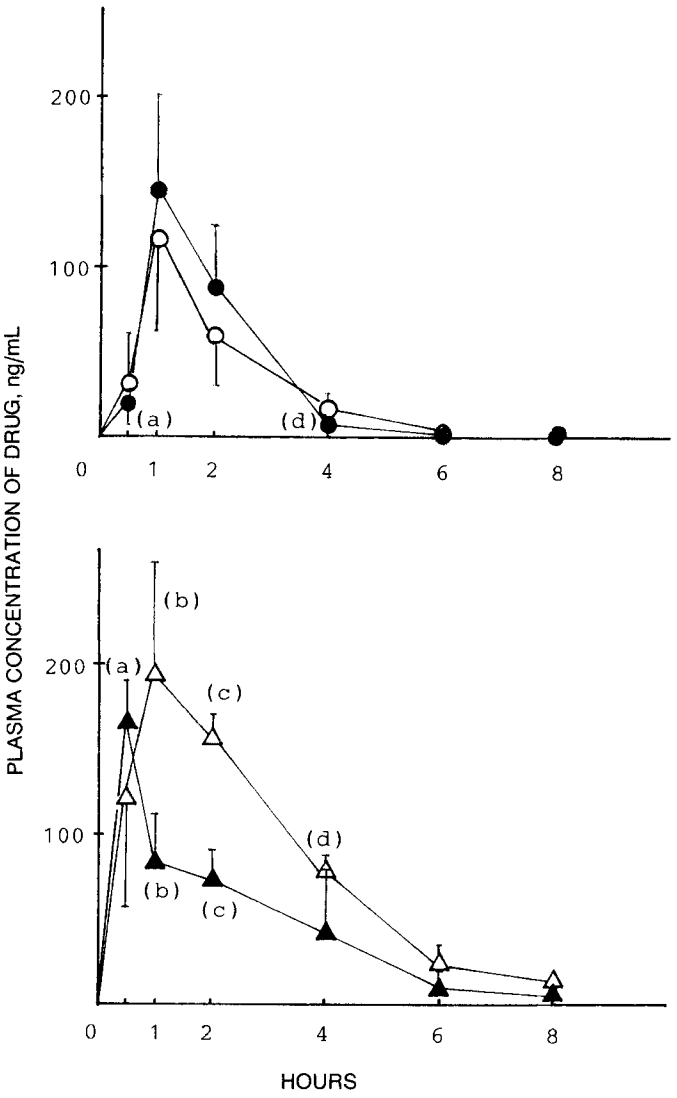


Figure 1—*Plasma concentration of cinnarizine following the oral administration to dogs of 50 mg of drug and its β-cyclodextrin complex (equivalent to 50 mg of drug) with or without 2 g of DL-phenylalanine. Each point represents the mean ± SEM of three dogs. Key: (●) cinnarizine alone; (○) cinnarizine with DL-phenylalanine; (▲) β-cyclodextrin complex alone; (△) β-cyclodextrin complex with DL-phenylalanine; (a) $p < 0.01$; (b–d) $p < 0.05$.*

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Figure 1 shows the mean plasma levels of CN following the oral administration of CN and CN/β-CD complex, with or without DL-phenylalanine, to dogs. At 0.5 h, the administration of CN/β-CD complex gave the maximum plasma level of 166.9 ± 22.4 ng/mL (mean ± SEM), which was 8.6 times as high as that of CN alone. This initial increase in drug absorption might be due to the high dissolution rate of the complex, i.e., 30 times as rapid as that of intact CN.[10] However, there was no significant difference between the areas under the plasma concentration–time curves (AUC) of CN alone and the CN/β-CD complex up to 8 h (267.2 ± 102.9 and 374.2 ± 97.2 ng·h/mL, respectively). This might be due to the large stability constant of the CN/β-CD complex, estimated to be $\sim 6.2 \times 10^3$ M^{-1} in water at 20°C,[10] resulting in a suppression of drug absorption, as the high dissolution rate of the complex mentioned above was not effective in enhancement of the AUC.

When CN was administered with DL-phenylalanine, there were no clear differences in the plasma level and AUC. On the other hand, the administration of the CN/β-CD complex with DL-phenylalanine brought about a clear increase in the plasma level and AUC ($p < 0.05$); the AUC values were 1.9 and 2.7 times as great as those of the CN/β-CD complex alone and CN alone, respectively. When the CN/β-CD complex was administered with DL-phenylalanine, the time of the peak blood concentration (1.0 h) was slightly later than when the CN/β-CD complex was administered alone. The reason for this is not clear at present, but it could be due to the difference in the method of administration, i.e., CN/β-CD in tablets and DL-phenylalanine in capsules (two tablets only in administration of CN/β-CD alone and two tablets and four capsules in administration of CN/β-CD with DL-phenylalanine).

These results indicate that DL-phenylalanine acts as a competing agent for CN in the CN/β-CD complex and increases bioavailability. The results also suggest that the pharmaceutical use of such competing agents might improve the therapeutic usefulness of drug–CD complexes.

References and Notes

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