Pharmacokinetics of Diltiazem and Its Metabolites in Dogs After Oral Administration of a Multiparticulate Sustained-Release Preparation

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Pharmacokinetics of diltiazem and its six metabolites were compared after oral administration in dogs of a multiparticulate sustained-release diltiazem preparation (HER-SR, QD) and a conventional diltiazem preparation (HER, TID). The plasma concentration of diltiazem, its two active basic metabolites (M1, N-monodesmethyl diltiazem; M2, deacetyl diltiazem), and four acidic metabolites [A1, (+)-(+)-(2S,3S)-2-(4-methoxyphenyl)-3-acetoxy-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-5-acetic acid; A2, 3-deacetyl-A1; A3, O-demethyl-A1; A4, O-demethyl-3-deacetyl-A1] following several administration routes were determined using high-performance liquid chromatography with UV detector (UV-HPLC). Following the oral administration of dogs, plasma concentrations were in the descending order of A2, diltiazem, M1, and M2. The absolute bioavailability of diltiazem was about 30%. Diltiazem conversion to its metabolites (M1, M2, A2) was 31.0, 2.1, and 14.6, respectively. Following intraduodenal and mesenteric venous administration of diltiazem, M1 and A2 were produced mainly in the intestine and liver. Oral administration of HER-SR and HER to dogs resulted in same plasma concentrations of A2, diltiazem, M1, and M2 (descending order). Supported evidence was the effective absorption of diltiazem from all gastrointestinal tract regions and similar formation ratios of diltiazem basic metabolites (M1, M2) from the duodenum, ileum, and colon.

KEY WORDS: diltiazem; sustained-release preparation; pharmacokinetics; metabolism; colon.

INTRODUCTION

Diltiazem is a coronary vasodilator, commonly referred to as a calcium channel blocker or calcium antagonist (1). It has a relatively short half-life of 4–5 hr and is usually administered three or four times daily. If the dosing frequency could be decreased, patient compliance might be improved, leading to improved therapy. Thus, attempts have been made to develop sustained-release preparations with an extended clinical effect. In this report we describe the pharmacokinetics of diltiazem and its metabolites after oral administration of a multiparticulate sustained-release diltiazem preparation (HER-SR; QD) (2) in dogs and compare it with a conventional diltiazem preparation (HER; TID).

After oral administration, diltiazem is metabolized to several basic or acidic metabolites, via pathways including O-deacetylation, N-demethylation, or oxidative deamination (3,4) (Fig. 1), but the pharmacokinetics have not been fully evaluated. Following intravenous administration of diltiazem and its metabolites, and oral administration of HER and HER-SR, plasma concentrations of diltiazem and its six metabolites were determined using a newly developed UV-HPLC method, and the metabolism of HER-SR in dogs is discussed.

EXPERIMENTAL

Materials

Chemicals. Diltiazem hydrochloride (Diltiazem), its metabolites [N-monodesmethyl diltiazem, M1; deacetyl diltiazem, M2; (+)-(2S,3S)-2-(4-methoxyphenyl)-3-acetoxo-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-5-acetic acid, A1; 3-deacetyl-A1, A2; O-demethyl-A1, A3; O-demethyl-3-deacetyl-A1, A4], and internal standard [cis-(2S,3S)-8-chloro-2-(4-hydroxy-phenyl)-3-acetoxo-2,3-dihydro-4-oxo-1,5-benzothiazepin-5-acetic acid] were synthesized in Tanabe Seiyaku Company. Other chemicals were special-grade reagents. As diltiazem preparation, a conventional diltiazem tablet containing 30 mg of diltiazem hydrochloride (HER; TID) and a multiparticulate sustained-release diltiazem capsule containing 100 mg of diltiazem hydrochloride (HER-SR; QD) were used for the study. The HER-SR preparation consisted of both fast (15% of total diltiazem) and slow (85%) release beads.

Animal Experiment

Animals. Four beagle dogs were purchased from Yoshiki-yakko and maintained on a diet of dog chow (Oriental yeast). The same dogs (12.8 ± 0.3 kg, mean ± SE; n = 4) were used in both intravenous and oral administration.

Intravenous Administration. An aqueous solution of 10–20 mg of diltiazem or its four metabolites (M1, M2, A1, A2) was administered intravenously to three dogs, and blood samples were withdrawn at 0, 3, 6, 9, 15, 30, 60, 120, 180, 240, and 360 min after administration.

Oral Administration. One tablet of HER or one capsule of HER-SR was administered orally to four dogs by compulsive swallowing with 30 mL of water. Blood samples were taken at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hr for HER and 0, 1, 2, 3, 4, 6, 8, 10, 13, 15, 17, 19, 21, 24, 27, and 30 hr for HER-SR.

Mesenteric Venous or Intraduodenal Administration. An aqueous solution of 10 and 30 mg of diltiazem was administered into the mesenteric vein and ligated upper intraduodenal loop (20 cm), respectively, of pentobarbital anesthetized dogs. Blood samples were withdrawn from a forelimb vein at 0, 3, 6, 9, 15, 30, 60, 120, 180, 240, and 360 min for the former and from the mesenteric vein at 0, 5, 10, 15, 30, 45, 60, 90, 120, 180, and 240 min for the latter.

Absorption and Metabolism of Diltiazem from Several Regions of the Gastrointestinal Tract. An aqueous solution of 30 mg of diltiazem was administered into the ligated intraduodenal, ileal, or colonic loops (20 cm) of pentobarbital-anesthetized dogs. Blood samples were withdrawn from a forelimb vein at 0, 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, and 300 min. Plasma samples were frozen at −20°C.

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Determination of Concentrations of Plasma Diltiazem and Its Metabolites

Plasma diltiazem and two basic metabolites (M1, M2) concentrations were determined by high-performance liquid chromatography (Shimadzu LC-3A) with UV detector (5). Plasma diltiazem acidic metabolites (A1, A2, A3, A4) were determined by high-performance liquid chromatography with UV detector as follows.

A 1 mL of plasma specimen was put into a 15-mL test tube containing 0.5 mL of internal standard (400 ng/mL) and 0.5 mL of 1 N HCl. To the test tube, 6 mL ethyl-n-octylalcohol (4:1) was added, then the test tube was shaken for 10 min. After 5 min of centrifugation, 5 mL of the organic phase was transferred into a 10-mL tapered tube, and 0.3 mL of a 0.07 M phosphate buffer solution (pH 8) was added, then the solution was mixed for 1 min. By this reverse extraction, A1, A2, A3, and A4 were transferred into the aqueous phase. After centrifugation for 5 min, the organic phase was discarded. The buffer solution was washed with 5 mL of n-hexane by mixing for 1 min. After centrifugation for 5 min, the organic phase was discarded. This washing procedure was performed again. After the aqueous solution was added with 50 μL of 1 N HCl, 200 μL of the aqueous solution was injected into the UV-HPLC. Conditions of HPLC for A1, A2, A3, and A4 were as follows: HPLC, Shimadzu LC-4A; detector, Shimadzu SPD-2A; column, Spherisorb 5-ODSII, 4.6 φ × 250 mm; mobile phase, 0.01 M phosphate buffer (pH 6.5): acetonitrile, 154:46 for A1 and A2 and 164:36 for A3 and A4; detection wavelength, 238 nm; flow rate, 0.5 mL/min; and column temperature, 50°C.

Inter- and intraassay coefficients of variation of diltiazem and its metabolites were <10%, and the limit of quantitation of diltiazem and its six metabolites was 5 ng/mL.

RESULTS AND DISCUSSION

Plasma Concentration After Intravenous Administration of Diltiazem to Dogs

The concentrations of plasma diltiazem and its six metabolites (M1, M2, A1, A2, A3, A4) after a single intravenous administration of 20 mg of diltiazem in aqueous solution to three dogs were determined for evaluation of diltiazem metabolism. Detectable plasma concentrations were in the descending order of diltiazem, A2, M2, and A1, while plasma concentrations of M1, A3, and A4 were below assay limits. The percentages of conversion of diltiazem to its metabolites (M2, A1, A2) were calculated to be 6.4, 4.8, and 1.8%, respectively, based on the AUCs of M2, A1, and A2 after intravenous administration of diltiazem or authentic metabolites. Table I shows the AUCs calculated from plasma levels of diltiazem and its metabolites.

Plasma Concentration After Oral Administration of a Conventional Diltiazem Preparation (HER) to Dogs

Table I also shows the AUCs calculated from plasma diltiazem and its four metabolites after an oral administration of a conventional diltiazem tablet (HER) to four dogs. Detectable plasma concentrations in descending order were found for A2, diltiazem, M1, and M2, while plasma concent-