Report

Performance of Diltiazem Tablet and Multiparticulate Osmotic Formulations in the Dog

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The in vivo performance of two extended-release (ER) osmotic formulations of diltiazem were evaluated in the beagle dog. Both ER formulations had similar bioavailabilities (F) as the diltiazem solution. Although F was somewhat variable following ER administration, this variability may be related to the drug entity since intra- and interanimal variability of orally administered diltiazem solutions was substantial. Deconvolution of the ER plasma diltiazem data with absorption data from the orally administered diltiazem solutions provided an estimate of the in vivo drug release from the ER formulations. The two ER formulations, designed with different in vitro release profiles, reflected these differences in vivo, with nearly identical respective in vivo and in vitro release profiles.

KEY WORDS: diltiazem; controlled release; deconvolution; dog; pharmacokinetics.

INTRODUCTION

Diltiazem is a potent calcium-channel blocker. By inhibiting calcium influx, diltiazem inhibits the contractile process of cardiac and vascular smooth muscle, thereby dilating the main coronary and systemic arteries (1). For the management of Prinzmetal variant angina and chronic angina pectoris, diltiazem has been available in the United States until recently only as a conventional dosage form, with 60 to 90 mg administered four times daily (2). If the dosing frequency were decreased, patient compliance might be improved, leading to improved therapy. Accordingly, the development of a sustained-release diltiazem formulation was initiated. This report summarizes the pharmacokinetics of intravenously and perorally administered solutions and the in vivo release rates of two extended-release osmotic formulations of diltiazem in the beagle dog. The in vivo release rates are compared with in vitro dissolution data.

MATERIALS AND METHODS

Dosage Forms

Two different extended-release (ER) dosage forms based on controlled porosity osmotic pump principles (3) were tested: a unit-dose osmotic tablet formulation and an osmotic multiparticulate formulation. The zero-order release rate of the ER tablet in phosphate buffer (0.05 M, pH 7.5) was calculated to be 7.3%/hr, releasing approximately 60% of the drug in 8 hr.

The ER multiparticulate formulation consisted of spherical particles (diameter range, 0.8–1.2 mm) which in phosphate buffer (0.05 M, pH 7.5) released 65% of the drug at ~11%/hr over a 6-hr period.

Analytical Method

Reagents and Standards. N-Desmethyl-diltiazem and N-ethyl-N-desmethyl-diltiazem were prepared from diltiazem (4). Acetonitrile, methanol, ethyl acetate, and methyl t-butyl ether were Burdick and Jackson high-purity solvents. Reagent-grade ammonium carbonate, dipotassium phosphate, and phosphoric acid were obtained from Mallinckrodt.

Instrumentation and Chromatographic Conditions. The HPLC system was equipped with an SSI Model 300 pump, a Perkin-Elmer ISS-100 autosampler, and a Kratos Model 783 spectrophotometric detector. Data were collected on an HP1000 minicomputer using Nelson Analytical Model 6000 software. Separations were performed on a Rainin Dynamax Microsorb CN column (4.6 mm × 25 cm with 5-cm guard column). The mobile phase was a solution composed of 1 part by volume acetonitrile/methanol (3:1) and an aqueous solution of dipotassium hydrogen phosphate (10 mM), adjusted to pH 7 with phosphoric acid. The column was operated at 30°C with a flow of 2.0 ml/min and the effluent was monitored at 237 nm. Retention times were 6.8 min for diltiazem, 9.9 min for the metabolite N-desmethyl-diltiazem, and 8.5 min for the internal standard.

Sample Preparation. Samples were processed quickly after thawing from a –20°C freezer to avoid hydrolysis of diltiazem. In a 5-ml centrifuge tube, 1.0 ml of plasma sample and 0.10 ml of internal standard (1 µg/ml in acetonitrile) were vortexed briefly, and 0.5 ml of 0.1 ammonium carbonate and 4 ml of 3:1 ethyl acetate/methyl t-butyl ether were added. The samples were extracted using a multitube vortexer. Af-
ter centrifugation, the upper layer was transferred from each tube into a second set of tubes containing 0.2-ml portions of an aqueous solution of phosphoric acid (0.2%). These tubes were vortexted to back-extract, then centrifuged, and the lower layer was taken cleanly for prompt analysis by injection of 50-μl aliquots into the HPLC.

**Standard Samples.** Working standard solutions were prepared by dissolving 10 mg each of diltiazem and N-desmethyldiltiazem in 10 ml of acetonitrile and sequentially diluting with acetonitrile. These solutions were stable when stored at −20°C. Drug-free plasma was spiked to contain 300, 100, 20, and 5 ng of diltiazem/ml. These samples were processed as above to generate the standard curve.

**Data Processing.** Peak areas of diltiazem, N-desmethyldiltiazem, and the internal standard (N-ethyl-N-desmethyldiltiazem) were measured for spiked plasma standards. Linear regression (r² > 0.99) of area ratios versus concentration produced standard curves for quantitation of both diltiazem and N-desmethyldiltiazem.

**Animal Studies**

Six beagle dogs (18.0 ± 1.7 kg) were administered either ER tablets, ER multparticles, a peroral solution on three occasions, or an intravenous (i.v.) solution on two separate occasions.

**Intravenous administration.** In the i.v. administration, 1 ml diltiazem solution (containing 18.3 mg diltiazem and 9 mg NaCl) was injected into each of the six dogs via the foreleg vein (i.v.-1). To mimic the peroral studies where it was desirable to maximize gastrointestinal retention of the peroral formulation, each dog was fed approximately 50 g of dog food before and every hour following diltiazem administration. Blood samples (3 ml) were taken from either the foreleg or the jugular vein immediately prior to dosing and 10, 20, 40, 60, 90, and 120 min and 4, 6, and 8 hr after administration and were centrifuged for the isolation of plasma and stored at −20°C until assayed. The i.v. administration was repeated (i.v.-2) in the same dogs approximately 5 months later.

**Peroral Dosing with Solution Administration.** One milliliter of solution (OS), containing 55 mg of diltiazem, was administered by peroral syringe into the back of the throat to the same six dogs. Blood samples (3 ml) were taken prior to dosing and at 0.5, 1, 2, 3, 4, 5, and 6 hr after administration, and they were assayed as described above. The OS administration was repeated in the same dogs approximately 2 and 5 months later.

**Peroral Dosing with Extended-Release Dosage Forms.**

One ER tablet containing 110 mg diltiazem was administered to each dog. Blood samples (3 ml) were taken prior to dosing and at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hr after administration and were assayed as described above. On a separate occasion, one capsule containing 110 mg diltiazem in the ER multiparticulate formulation was similarly administered. Blood samples were taken prior to dosing and 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hr after administration and assayed as described above.

**Pharmacokinetics**

Individual sets of i.v. diltiazem concentrations (C) were fitted to a two-compartment model [see Eq. (1)] using SIFPAR (SIMED, Créteil, Cedex-France) and a weight of 1:

\[
C_{TV} = Ae^{-\alpha t} + Be^{-\beta t}
\]

where \(t\) is time, and \(\alpha\) and \(\beta\) are fast and slow rate constants, respectively. Best fits were determined by using Akaike criteria and by minimizing the coefficient of variant (CV) associated with computed parameter estimates.

The parameter "area under the concentration versus time curve" (AUC) for individual dogs was calculated by the trapezoidal method and Eq. (2):

\[
AUC_{last} = C(last)/\beta
\]

where C(last) is the last plasma diltiazem concentration and \(\beta\) is the terminal disposition rate constant for the individual dog. Systemic clearance (Cl) was calculated by Eq. (3):

\[
Cl = \text{dose}/\text{AUC}
\]

Steady-state volume of distribution (\(V_{ss}\)) was estimated by Eq. (4):

\[
V_{ss} = \text{dose (AUMC/AUC)}^2
\]

where AUMC is the area under the first moment curve. The individual plasma diltiazem concentrations following administration of the peroral solutions and ER dosage forms were deconvoluted (SIFPAR) against the i.v. data using the point area method (5). The software interpolates the existing data to arrive at equally spaced and identical time intervals following OS, ER, and i.v. during the absorption phase. Next SIFPAR calculates AUC for each interval of the OS and ER data and deconvolutes this against the i.v. concentration corresponding to each interval, to arrive at the fraction absorbed during each interval. By visually inspecting the fraction absorbed versus time data plotted on linear or log-linear coordinates, an absorption rate order can be approximated. For the ER data, the relationship appeared zero order, and the slope yielded the in vivo release rate (\(k_{0,abs}\)); for the OS-2 data, the relationship was more obscure (see below). The ER data were similarly deconvoluted against the OS data, again resulting in in vivo release rates (\(k_{0,in vivo}\)). The apparent in vivo release rates of the ER dosage forms were estimated by linear regression of the initial slope of the percentage diltiazem absorbed versus time curves.

Comparisons were made with ANOVA and differences (least significant difference or Student–Newman–Kuel) were considered significant at \(P < 0.05\) (6). All data are presented as mean ± standard deviation.

**RESULTS AND DISCUSSION**

Every i.v. plasma concentration versus time profile exhibited nearly identical biexponential characteristics (Table I). The terminal elimination half-life (\(t_{1/2,\beta}\)) in the i.v. study (2.7–3.2 hr) was similar to the 2.2- to 3-hr half-life previously reported by others (7,8). The \(V_{ss}\) (114–124 liters) in this study was also similar to that reported (8) earlier (137 ± 20 liters); however, the CI was slightly less (500–566 vs 830 ± 86 ml/min).

The initial OS plasma data set (OS-1) and those obtained following repeated studies in the same dogs 2 months (OS-2)