Mechanism of Compound- and Species-Specific Food Effects of Structurally Related Antiarrhythmic Drugs, Disopyramide and Bidisomide

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Purpose. To determine mechanism of food effects observed with bidisomide but not with the structurally similar drug, disopyramide.

Methods. Food effect studies of bidisomide and disopyramide were conducted with and without a standardized high fat meal in healthy subjects and in the dog. Intestinal metabolism of disopyramide and absorption of the metabolites were examined after oral administration of the drug to the dogs with portal vein canula implanted. Effects of food or a mixture of amino acids on metabolism of [14C]disopyramide were examined after intraperitoneal infusion of the drug with and without high fat meal and after drug infusion into portal vein with the amino acid mixture, respectively.

Results. The systemic availability of bidisomide was markedly reduced with food in humans, whereas the systemic availability of disopyramide did not change notably. In the dog, the systemic availability of bidisomide was also reduced with food. The systemic availability of disopyramide did not change with food. This was due to the fact that reduction in absorption was compensated by reduction of metabolism. There was no evidence for reduction in hepatic and intestinal metabolism with food.

Conclusions. The apparent reduction in disopyramide metabolism with food may be due to an increase in colonic and/or lymphatic absorption. Food effects on the apparent systemic availability of bidisomide and disopyramide in the dog were similar to those in the rat. However, there was substantial species difference in the mechanism of food effects.

KEY WORDS: food effect; bidisomide; disopyramide; dog; species difference.

INTRODUCTION

Food can have marked effects on drug absorption by increasing, decreasing, or sometimes simply delaying it. These food effects are due to many factors such as direct binding of a drug to food components or changes in metabolism, luminal pH, gastric emptying, intestinal transit, mucosal absorption and splanchnic-hepatic blood flow (1–6). Although there are many drugs whose bioavailability is affected by food, there have been very few investigations on the mechanism and species difference of those food effects.

Disopyramide is widely used as a quinidine-like (1C) antiarrhythmic drug (7). Bidisomide is an antiarrhythmic agent (8) which is structurally similar to disopyramide. Despite the similarity in chemical structure of these compounds, their absorption characteristics and food effects are remarkably different. The systemic availability of bidisomide was approximately 20%, 67% and 40% in the rat, dog and man, respectively, when the drug was administered orally after overnight fasting (8–10). However, the systemic availability of bidisomide was greatly reduced in the rat, dog and man when administered with food (11,12). The systemic availability of disopyramide in the rat, dog and man were 46%, 70% and >80%, respectively (11,13,14), and not markedly affected with food in these species. The present study was conducted to explore reasons for the differences in food effects of these structurally similar compounds using the dog as an animal model.

MATERIALS AND METHODS

Materials

[14C]Disopyramide (lot No. GDS4361-19, specific activity of 41.1 μCi/mg), [14C]bidisomide (lot No. GDS-1840-134, specific activity of 38.9 μCi/mg), unlabeled disopyramide and bidisomide were obtained from G. D. Searle & Co. All other chemicals used were commercially available.

Animal Study

A comparative food effect study with [14C]bidisomide and [14C]disopyramide was conducted as follows: Four female beagle dogs weighing 8-11 kg received [14C]bidisomide or [14C]disopyramide orally as a solution after overnight fasting or with a high fat meal in a cross-over manner. The high fat meal was composed of 2 slices of toasted white bread with butter, two eggs fried in butter, 2 slices of bacon, 2 ounces of hash brown potatoes, and 8 ounces of whole milk. Each plasma sample was analyzed for total radioactivity. For determination of the parent drug concentrations, an equal volume of plasma was pooled from each dog and combined for a given time point. The pooled plasma samples were analyzed for [14C]bidisomide and [14C]disopyramide using an HPLC procedure.

Four male mongrel dogs which were implanted with a chronic portal vein access port (CPVAP) were administered an oral dose (10 mg/kg) of [14C]disopyramide with and without the high fat meal in order to examine whether intestinal metabolism of disopyramide changed with food or not. Blood samples were collected from both portal and cephalic veins at specified time points. A liver metabolism study of [14C]disopyramide was conducted in female beagle dogs which were implanted with the CPVAP. Three female dogs received an iv infusion dose (10 mg/kg) of [14C]disopyramide via the CPVAP over a 30 min period starting at 30 min after feeding the high fat meal and the other two dogs received the iv infusion dose via the CPVAP 1 h after feeding. After a washout period of at least one week was allowed, all five dogs received an iv dose of [14C]disopyramide via the CPVAP after overnight fasting to compare the extent of liver metabolism with and without food. In addition, three dogs also received the 30 min iv infusion dose of [14C]diso-
pyramide via the CPVAP with and without Aminosyn II® (Abbott laboratories, North Chicago, IL) containing approximately 150 mg total amino acids and 0.6 mg sodium hydrosul-

fite/ml. In these studies, blood samples were collected from the cephalic vein at selected time points during and after the infusion.

Clinical Study

Disopyramide

Healthy male subjects between 19 and 40 years of age participated in the study. Prior to inclusion, subjects underwent a full medical examination and routine, clinical laboratory tests of biochemistry and hematology and gave written consent to participate. Sixteen subjects received two 150 mg Norpace CR capsules (Lot No. 384-039) four hours before or immediately after a standardized meal (the same as in the dog study) in a randomized cross over manner. A washout period of seven days separated the treatment. Blood samples were collected at specified time points.

Bidisomide

Sixteen subjects received the following treatments (Treatment A and B) in a randomized cross over manner. Bidisomide was administered at a single dose of two 200 mg tablets (Lot No. RTC#9427) on day 1 and every 12 h for study days 2-6. For Treatment A, subjects received their doses of bidisomide in the fasted condition on days 1-6. For treatment B, subjects received their doses of bidisomide within 15 min of the meal. The two treatments were separated by a 6-9 day washout period. For each treatment, plasma samples for bidisomide analysis were obtained at predetermined intervals on study day 1 (single dose) and study day 6 (steady state).

Sample Analysis

For concentrations of total radioactivity in plasma, aliquots (100 µl) of each sample were mixed with 10 ml of Aquassure (DuPont Co., Boston, MA) and the carbon-14 concentrations were determined by liquid scintillation counting (LSC) using liquid scintillation spectrometers (Mark III, Tracor Analytic, Elk Grove, IL).

Concentrations of bidisomide in human plasma were determined using a gas chromatographic (GC) procedure (9). Concentrations of [14C]bidisomide in dog plasma were determined by HPLC. Concentrations of disopyramide in human serum were determined using a homogenous enzyme assay, EMIT Disopyramide Assay Kit (Syva Co., Palo Alto, CA). Concentrations of [14C]disopyramide in dog plasma were determined by HPLC.

HPLC

HPLC was performed on a Hewlett-Packard HPLC (Hewlett-Packard GmbH, F.R.G.) equipped with HP series 1050 pumps, 1050 auto-injector and a C-18 Radial-Pak liquid chromatography cartridge (8 mm ID, 10 micron particle size). For quantitation of [14C]bidisomide, a linear gradient system was employed from 5% methanol in 0.01M dibutylamine phosphate (DBAP) to 90% methanol in 0.01M DBAP over a 60 minute period. The flow rate of the mobile phase was 1.5 ml/min. For quantitation of [14C]disopyramide in dog plasma, an isocratic condition was used with the mobile phase of water, acetonitrile, methanol, and pH 2.5 (1 M) DBAP (70, 19, 10, 1, V/V). The flow rate of the mobile phase was 1 ml/min. The eluent from the HPLC was collected every 0.5 min and each fraction was counted for radioactivity using the LSC procedure.

RESULTS

Clinical study

Fig. 1 shows mean plasma concentration-time curves for bidisomide and disopyramide after single dose administration (day 1) under fasting and fed conditions. The mean (SD) AUC0–72h value of bidisomide under fed conditions (6.34 ± 2.31 µg-h/ml) was approximately 54% of that (10.9 ± 2.6 µg-h/ml) under fasted conditions and these AUC values were significantly different (p < 0.05). Following repetitive dose (400 mg) administration every 12 h for five additional days, the AUC(0–72h) values with and without food were 6.76 ± 2.08 and 13.0 ± 3.8 µg-h/ml and were also significantly (p < 0.05) different. The food effects observed at the steady state (day 6) were similar to those after single dose administration.

The mean AUC0–72h value of disopyramide under fasting and non-fasting conditions were 36.2 ± 14.1 and 38.7 ± 10.8 µg-h/ml and these values were not significantly different (p < 0.05). Thus, apparent systemic availability of the drug was, on average, not affected by the high fat meal.

Dog Studies

After oral administration of [14C]bidisomide to the beagle dog as an aqueous solution, the AUC values of total radioactivity with and without food (22.1 ± 3.4 and 36.5 ± 3.4 µg eq hr/ml, respectively) were significantly (p < 0.05) different (Fig. 2). The AUC values of the parent bidisomide in pooled plasma with and without food were 19.9 and 30.7 µg-hr/ml, respectively. The systemic availability of total radioactivity and bidisomide with food was approximately 60 and 65%, respectively, of those without food. These results are consistent with findings after oral administration of a 200 mg tablet to the dog (12).

After [14C]disopyramide administration to the beagle dog, the AUC values of total radioactivity with and without food were 38.3 ± 4.1 and 53.1 ± 4.8 µg eq-h/ml, respectively, and

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