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 [^{14}C]disopyramide were examined after intraportal 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 colonal 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

[^{14}C]Disopyramide (lot No. GDS4361-19, specific activity of 41.1 μCi/mg), [^{14}C]bidisomide (lot No. GDS-1840-134, specific activity of 38.9 μg/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 [^{14}C]bidisomide and [^{14}C]disopyramide was conducted as follows: Four female beagle dogs weighing 8-11 kg received [^{14}C]bidisomide or [^{14}C]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 [^{14}C]bidisomide and [^{14}C]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 [^{14}C]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 [^{14}C]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 [^{14}C]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 [^{14}C]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 [^{14}C]diso-

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pyramide via the CPVAP with and without Aminosyn II^R (Abbott laboratories, North Chicago, IL) containing approximately 150 mg total amino acids and 0.6 mg sodium hydrosulfite/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 [^{14}C]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., Plao Alto, CA). Concentrations of [^{14}C]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 [^{14}C]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 [^{14}C]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) AUC_{0-24h} 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_{0-12h} 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 AUC_{0-72h} 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 [^{14}C]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 [^{14}C]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

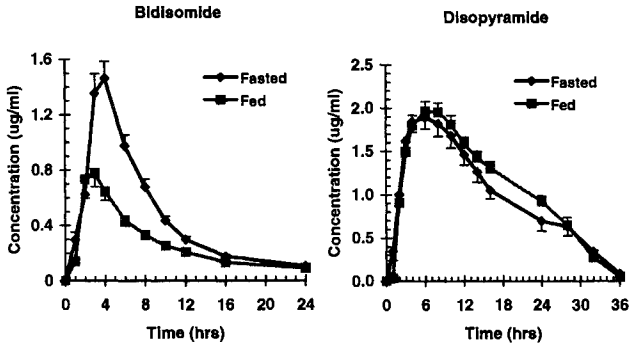

Fig. 1. Mean (SE) plasma concentration-time curves for bidisomide and disopyramide after oral administration of bidisomide or disopyramide to healthy subjects under fasted and fed conditions.

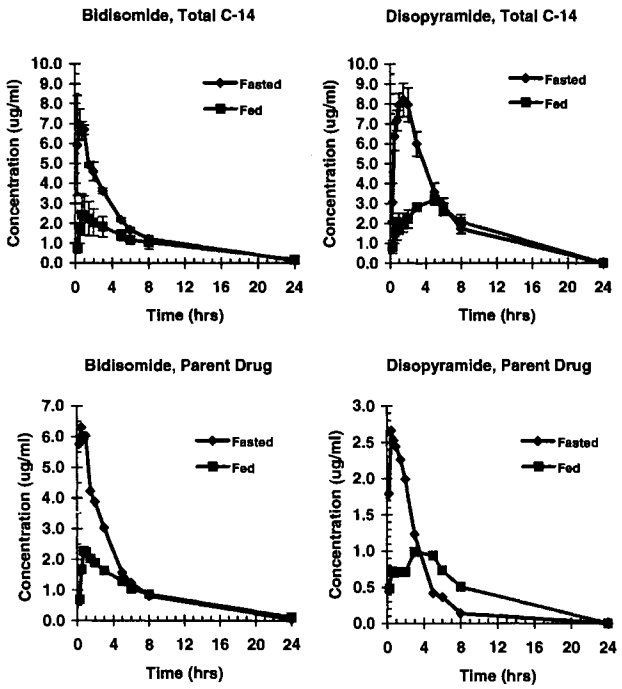

Fig. 2. Mean (SE) plasma concentration-time curves for total radioactivity (top panels) and concentrations of bidisomide (bottom left panel) and disopyramide (bottom right panel) in pooled plasma after oral administration of [^{14}C]bidisomide or [^{14}C]disopyramide to the dog under fasted and fed conditions.

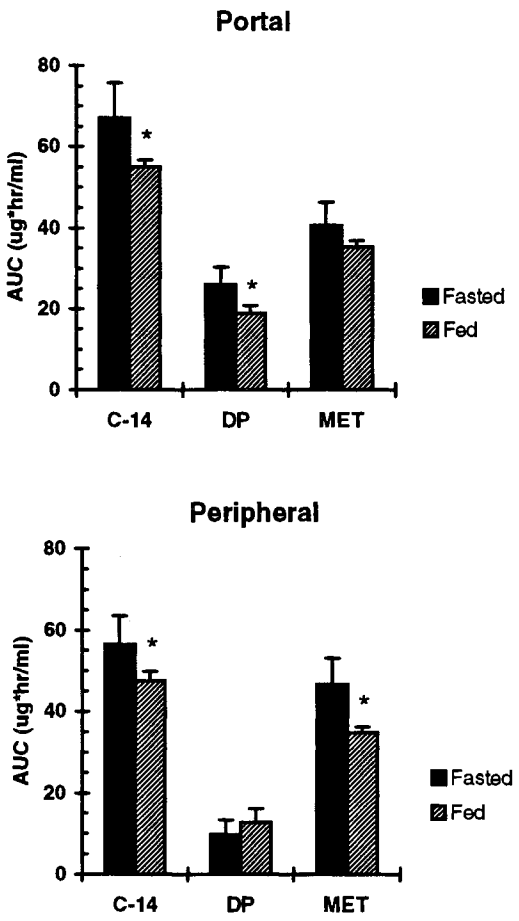

Fig. 3. Mean (SE) AUC of total radioactivity, disopyramide and total metabolites after oral administration of [^{14}C] disopyramide to the mongrel dogs. Asterisks indicate statistical significant ($p < 0.05$) difference between the fasted and fed groups.

absorption of disopyramide was also significantly ($p < 0.05$) reduced with food (Fig. 2). In contrast to total radioactivity data, the AUC of disopyramide was similar with and without food (10.3 and 9.6 μg·hr/ml, respectively).

After oral administration of [^{14}C]disopyramide to the mongrel dogs with portal vein cannula implanted, the AUC values for total radioactivity in both portal and peripheral plasma were significantly ($p < 0.05$) greater without food than with food (Fig 3). Furthermore, the AUC values for disopyramide in portal plasma were also substantially greater without food than with food. These results as a whole indicate that absorption of disopyramide was reduced with food. The AUC values of disopyramide in peripheral plasma with and without food were not significantly different.

Concentrations of disopyramide were greater in portal plasma than in peripheral plasma in the early time points regardless of food conditions and AUC values were significantly ($p < 0.05$) higher in portal plasma than in peripheral plasma. This was due to absorption of disopyramide in the GI tract. However, concentrations of total metabolites (mono- and Di-N-dealkylated metabolites) in portal plasma never exceeded peripheral plasma concentrations at any time points with or without food (Fig. 4). These results suggest that there was no absorption of possible intestinal metabolites regardless of food conditions. If metabolites were formed in the GI lumen and/or tissues and were absorbed into portal blood, concentrations of metabolites were expected to be higher in portal plasma than in peripheral plasma in the absorption phase.

After oral administration of [^{14}C]disopyramide, the ratios of total metabolites/disopyramide in plasma were the same with and without food at 1 h (Fig. 5). However, the ratios were significantly greater without food at later time points (e.g. 7 h). When [^{14}C]disopyramide was directly infused via portal vein, the ratios of metabolites/drug were similar with and without food at all time points and there was no evidence for apparent metabolism changes with food (Fig. 5). When [^{14}C]disopyramide was injected into portal vein together with the mixture of amino acids, there were also no notable changes in the extent of metabolism.

DISCUSSION

The present study demonstrated that the structurally similar bidisomide and disopyramide exhibit remarkably different food effects in humans and the dog. The systemic availability of bidisomide was markedly reduced with food, but the systemic availability of disopyramide did not change significantly with food in humans. Similar phenomena were observed in the dog in the present study as well as in the earlier study (12) and also in the rat study (11).

Although similar food effects of these compounds were demonstrated in the rat and dog, as in humans, there were substantial differences in the mechanism of food effects in these species. In the rat, the differences in food effects on the systemic availability of the parent drugs between bidisomide and disopyr-

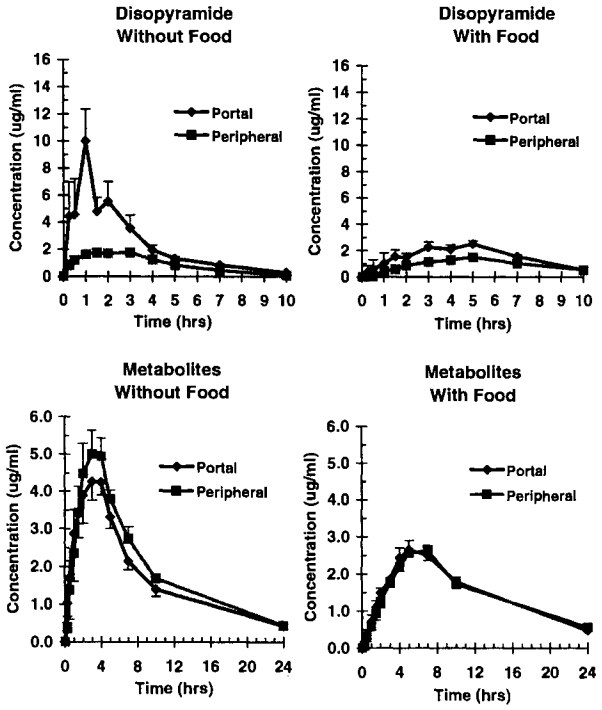

Fig. 4. Mean (SE) concentration-time curves for disopyramide and total metabolites in portal and peripheral plasma after oral administration of disopyramide to the dog under fasting and non-fasting conditions.

amide was due to the fact that absorption of bidisomide was reduced with food, whereas absorption of disopyramide did not change. There was no notable changes in metabolism of either compound with food in the rat. Reduction in bidisomide absorption in the rat may be due to multiple factors. However, lower intestinal permeability of bidisomide compared to disopyramide and greater inhibition of bidisomide absorption by amino acids and dipeptides could, at least in part, account for the differences in food effects between the two compounds.

In contrast to the rat, absorption of both bidisomide and disopyramide was reduced with food in the dog even though reduction of disopyramide absorption was less pronounced (15–25%) compared to bidisomide (approx. 40%). The major difference in food effects of bidisomide and disopyramide in the dog is due to the fact that the extent of bidisomide metabolism did not change with food, whereas the overall extent of disopyramide metabolism was significantly reduced with food, compensating for the reduction in absorption. This resulted in no apparent food effects on the systemic availability of disopyramide in the dog. The apparent reduction in disopyramide metabolism with food was not due to changes in intestinal or hepatic metabolism. In the portal vein cannulated dog study, there was no evidence for absorption of possible intestinal metabolites. Thus, any changes in the intestinal metabolism would not account for the reduction in the ratios of metabolites/disopyramide in plasma with food. Furthermore, when hepatic metabolism of disopyramide was examined after direct injection of the drug into the portal vein with and without the high fat meal, there was no evidence that food reduced liver metabolism of the drug. Therefore, the apparent reduction in disopyramide metabolism, when the drug was administered orally with food, may be due to enhancement of lymphatic and/or colonic absorption which partially bypasses the first pass liver metabolism. This hypothesis is further supported by the fact that the differences in the ratios of metabolites/drug in plasma between fasting and nonfasting conditions were the same at 1 h after feeding and there was no evidence for metabolism changes. However, the metabolism was markedly reduced at the later time points (e.g. 7 h), at which food absorption has been long completed and any direct food effects on metabolism are not expected (Fig. 5). If food directly inhibited the hepatic metabolism of disopyramide, inhibition of metabolism would be more pronounced at 1 and 3 h after dosing with meal than at 7 h. Disopyramide is less soluble (1 mg/ml) than bidisomide (10 mg/ml) in water (12). Thus, it is conceivable that disopyramide is better solubilized in the presence of high fat than bidisomide, possibly increasing lymphatic and/or colonic absorption.

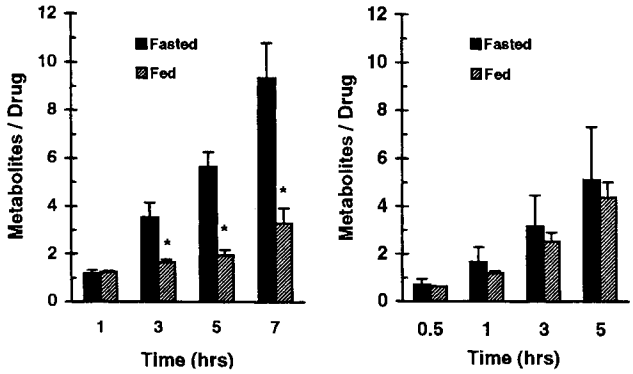

Fig. 5. Mean (SE) ratios of metabolites/disopyramide in dog plasma after oral (left panel) and intraportal (right panel) administration with and without food. Asterisks indicate statistical significant ($p < 0.05$) difference between the fasted and fed groups.

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