Reduced Systemic Availability of an Antiarrhythmic Drug, Bidisomide, with Meal Co-administration: Relationship with Region-Dependent Intestinal Absorption

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Purpose. The aim of this research was to determine the mechanism by which a co-administered meal decreases the oral absorption of bidisomide and does not influence the oral absorption of the chemically-related antiarrhythmic agent, disopyramide.

Methods. Bidisomide plasma levels, following oral administration and intravenous infusion in the fasted state and with various meal treatments, were determined in human subjects. A dialysis technique was employed to examine the potential for drug binding to meal homogenates. Plasma levels, following drug administration through duodenal and jejunal intestinal access ports and following various meal treatments with oral drug co-administration, were compared for bidisomide and disopyramide in a canine model.

Results. Bidisomide plasma AUC was significantly reduced following oral drug co-administration with breakfast compared to fasted-state controls in human subjects and in dogs independent of the composition of the solid cooked breakfast. While intravenous bidisomide infusion in human subjects showed a statistically significant reduction in AUC 15 minutes after oral administration of a high fat breakfast as compared to drug infusion in the fasted state, the reduction (–13%) was substantially smaller than the reduction (from –43% to –63%) observed with oral bidisomide meal co-administration. The percentages of bidisomide and disopyramide lost by binding to homogenates of cooked breakfast were 25.0 ± 5.7% and 23.7 ± 7.7%, respectively, as determined by dialysis at 4 hours. In dogs, the extent of absorption of disopyramide was comparable from oral, duodenal and mid-jejunal administration while the extent of bidisomide absorption from mid-jejunal administration was significantly lower than for oral or duodenal administration. Non-viscous liquid meals decreased C_{max} but not AUC, while viscous homogenized solid meals decreased both C_{max} and AUC for bidisomide with oral drug-meal co-administration. Oral non-caloric hydroxypropyl methylcellulose meals decreased bidisomide to the same extent as homogenized solid meals but did not lower disopyramide AUC.

Conclusions. The significant reduction in bidisomide plasma levels observed with meal co-administration in human subjects was predominantly mediated through a reduction in drug absorption and was independent of solid meal composition. The difference in meal effect on the absorption of the two drugs in humans did not appear to be a function of drug binding to cooked meal components over typical human upper gastrointestinal residence times. In dogs, the high-viscosity medium generated by oral co-administration of a solid meal reduced the upper intestinal absorption of bidisomide and disopyramide. Bidisomide AUC was decreased since it was well absorbed in the upper but not lower small intestine. Disopyramide AUC was not significantly affected since it was well absorbed from both regions. A similar mechanism may play a role in drug plasma level reductions following oral co-administration with solid meals for drugs showing similar regionally-dependent absorption profiles.

KEY WORDS: drug absorption; food effects; site-specific absorption; regional-dependent absorption; intestinal clearance; viscosity; bidisomide; disopyramide; canine model.

INTRODUCTION

Disopyramide is an antiarrhythmic agent that has been on the market in an oral dosage form since 1969. The absolute bioavailability of disopyramide in man is 60–90% and the extent of oral absorption of disopyramide is not substantially effected by simultaneous ingestion of food (1). Five-day excretion of ^{14}C-disopyramide following oral administration in man is 80% in the urine primarily as the parent drug (2). Bidisomide, an antiarrhythmic agent which is structurally related to disopyramide, has an absolute bioavailability of 45–62% in man and oral co-administration with a standard breakfast reduced the relative oral bioavailability 63% in a clinical study (3,4). Five-day excretion of ^{14}C-bidisomide following oral and intravenous administration in man is 60% and 41%, respectively, in the feces (2). Less than complete systemic bidisomide availability from oral administration is due to incomplete absorption. This projection is based on the following facts. 1) Metabolism in man is not extensive (4). 2) The percentage of parent drug eliminated in urine is not appreciably different following intravenous and oral administration (5). 3) More parent drug is found in the feces after oral administration compared to intravenous administration (5).

A negative food effect on bidisomide plasma levels, following oral administration, is also observed in rat and dog. In rat, bidisomide oral bioavailability is only 20–25% and, in a recent report (6), the negative food effect on bidisomide absorption in rats was suggested to be related to lower bidisomide permeability in rat ileum as compared to disopyramide permeability. Similar to humans, a negative food effect on disopyramide is not observed in rats. In the dog, bidisomide oral bioavailability is 60–70% and an earlier t_{max} is observed as compared to human and rat (7).

In this study, the role of meal composition was studied in humans and dogs. Based on the fact that the negative food effect was independent of caloric content and the bidisomide plasma level reduction was similar in both species, mechanistic studies were explored in a canine model. The fact that negative food effects were not observed with disopyramide permitted a reasonable mechanistic comparison study. Following some preliminary studies in dogs to probe the nature of the food effect, it was determined that a difference existed for liquid versus solid meals. This led to a study on the connection between meal viscosity and the potential for regional differences in the absorption of these two drugs.

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MATERIALS AND METHODS

Materials

Bidisomide and disopyramide were supplied by G. D. Searle & Co. (Skokie IL). Hydroxypropyl methylcellulose (HPMC, Methocel®) was supplied by Dow Chemical Co., Midland, MI. All other chemicals were commercially available.

Study Protocol

Human Meal Composition Studies

Sixteen male subjects, 19–39 years of age, completed this open label, randomized, balanced, four period, single dose crossover study. Following an overnight fast, a single dose of two 200 mg tablets was administered orally with 180 mL of water in the fasted state or immediately following completion of a high-fat (HF: 1000 calories containing 75 g fat, 33 g protein and 58 g carbohydrate), medium-fat (MF: 500 calories containing 8 g fat, 17 g protein, 103 g carbohydrate) or low-fat (LF: 250 calories containing 1 g fat, 12 g protein, 51 g carbohydrate) breakfast with a four-day washout period between treatments. Blood samples were drawn up to 48 hours post-dosing. Detailed meal compositions are provided in Table I.

Human Intravenous Infusion Studies

Twelve male subjects, 22–44 years of age, completed this randomized single dose crossover study. Treatments included 150 mg of bidisomide, infused over 30 minutes, in the fasted state and 15 minutes after finishing a high-fat breakfast with a six-day washout period. Both the fasted-state and HF breakfast conditions were the same as those outlined in the meal composition study except that 180 mL of water was not administered. Blood samples were drawn up to 24 hours after initiation of dosing.

Drug Binding Studies with Meal Homogenate

In vitro binding studies of 10 mg/ml bidisomide and disopyramide were carried out using a dialysis method. The ingredients from the cooked high-fat breakfast listed in Table I were homogenized and 9 mL of the food preparation or phosphate buffer (controls) was then added along with 1 mL of drug solution into appropriate length dialysis tubing with 6000–8000 molecular weight cut off (Spectra/Por 1®). The dialysis tubes were tied and placed individually in 60 mL amber bottles containing 20 mL of phosphate buffer (pH 7.0). The bottles were capped tightly and placed in a 37°C shaking water bath.

Canine Meal Composition Studies

Oral administration of one 200 mg bidisomide tablet after an overnight fast or with the same high, medium and low-fat meals administered in the human meal composition studies was carried out in four female beagle dogs, weighing 8–11 Kg, in a 4-way cross-over design. Meals were cooked and then homogenized immediately prior to co-administration with drug by gastric tube. In contrast to the human studies, an additional 180 mL of water was not administered with the tablet in the fasted state or immediately following the meals. The fluid volume co-administered with bidisomide tablets in the fasted state control study was 5 mL/kg dog weight. Blood samples were obtained up to 8 hours post-dosing.

Absorption Site Study in Dogs

Oral administration, and duodenal and mid-jejunal infusion of 15 mg/ml bidisomide and disopyramide after an overnight fast were carried out in four male beagle dogs, weighing 9.1–15.5 kg, in a crossover fashion with a one week washout period. Duodenal and jejunal intestinal access ports (Access Technologies, Skokie, IL) were surgically implanted in each dog. In the oral study, bidisomide or disopyramide free base was dissolved in 200 ml of water and the drug solution was administered directly into the stomach through a gastric tube. In the intestinal administration studies, drug was dissolved in 200 ml of 10 mM MES buffer (pH 6.5, 400 ± 20 mOsm/Kg). Drug solutions were infused at a rate of 3.8 mL/min through intestinal access ports directly into the duodenum or mid-jejunum. This infusion rate is in the upper range for fed-state and lower range

Table I. Meal Composition of High Fat, Medium, and Low Fat Meals

Type of meals	Meal Compositions
High fat meal	2 slices of toasted white bread spread with butter 2 eggs fried in butter 2 slices of bacon 2 ounces of hash brown potatoes 8 ounces of whole milk
Medium fat meal	1 slice of toasted white bread spread with peanut butter and jelly 1 ounce of dry cereal (corn flakes) 1 banana 6 ounces of orange juice 8 ounces of skim milk
Low fat meal	1 slice of white bread spread with jelly 6 ounces of orange juice 8 ounces of skim milk

for fasted-state transit rate in the canine upper small intestine (8). Blood samples were taken up to 8 hr after administration of drug.

Meal Effect Study

Two equivalent-calorie (250 Kcal) and equivalent-composition meals, liquid nutrient versus homogenized solid nutrient, were utilized in three male beagle dogs weighing 9.1–15.5 Kg. Liquid meal was prepared by dissolving bidisomide in an enteral nutrient liquid (Ensure®, 250 Kcal/8 oz.). Solid nutrient meals were prepared by homogenizing a portion of canned dog food (P/D Hill's®) containing 250 Kcal with bidisomide solution. Following an overnight fast, test meal solutions were administered directly into the stomach through a gastric tube. Blood samples were collected up to 12 hours.

Mechanistic Study

Based on the results of the absorption site and meal effect studies, the effect of meal viscosity was studied in three healthy male beagle dogs to explore the impact of this meal characteristic on the effect of food on bidisomide absorption. Bidisomide and disopyramide test solutions at 15 mg/ml were made up with 2% HPMC dissolved in 10 mM MES buffer (pH 6.5, 400 ± 20 mOsm/Kg) prepared by a "hot/cold" technique (9). Both drugs are stable throughout the preparation processes. The viscous solution was prepared using blends of K4M and K15M premium grade HPMC with the ratio of (2.36/3.64) in an attempt to mimic the viscosity of the homogenized solid meal. Rheological profiles were measured over 100–1000 s^{-1} at 37 °C on a Contraves Rheomat 135-S viscometer (Cincinnati, Ohio). Following an overnight fast, test solutions were administered directly into the stomach via gastric tube. Blood samples were collected up to 12 hours.

Sample Analysis

Plasma concentrations of bidisomide or disopyramide were measured by HPLC. A Brownlee® 5-μm CN column was utilized for separation. The mobile phase was prepared by mixing acetonitrile and an aqueous solution of 20 mM monosodium phosphate (pH 4.0) in the ratio 50:50. The flow rate was 1.0 ml/min and a UV detector was employed at a wavelength of 207 nm. For disopyramide analysis, bidisomide was used as an internal standard. For bidisomide analysis, disopyramide was used as an internal standard.

Sample Preparation

Plasma samples were alkalinized with 1 N NaOH and extracted with one mL of chloroform. The organic layer was transferred to a clean test tube after centrifugation, and evaporated to dryness under a stream of dry nitrogen. The samples were reconstituted with 200 μl of mobile phase and a 50 μl portion was then injected onto the HPLC. The limit of detection of both drugs was 0.05μg/mL. The standard curve linear correlation coefficients were both higher than 0.999 and the percentage of coefficients of variation (CV) of the between-day assay of standards for the standard curve for both drugs were approximately 10%.

Statistical Analysis

The area under the drug plasma concentration-time curve (AUC, μg · hr/mL) was obtained using the trapezoidal rule. Peak plasma concentration (C_{max}, μg/mL), and time to maximum concentration (t_{max}, min.) values were estimated directly from raw data. One way analysis of variance was performed to assess treatment differences using Sigma Statistic® in Sigma Plot® software. If the overall F test for treatment differences was significant ($p < 0.05$), then multiple comparisons were performed to investigate the nature of these differences.

RESULTS

Human Meal Composition Studies

Bidisomide plasma levels and both C_{max} and AUC were significantly lower with co-administration of each of the meal treatments as compared to fasted-state control studies (Fig. 1(A) and Table II). The AUC was decreased 22.17%, 47.49%, and 30.89% after co-administration of bidisomide with high, medium, and low fat meals, respectively, as compared to fasted-state.

Human Intravenous Infusion Studies

Mean bidisomide plasma level AUC from intravenous drug infusions, 15 minutes after oral administration of the same high fat breakfast utilized in the oral meal composition study,

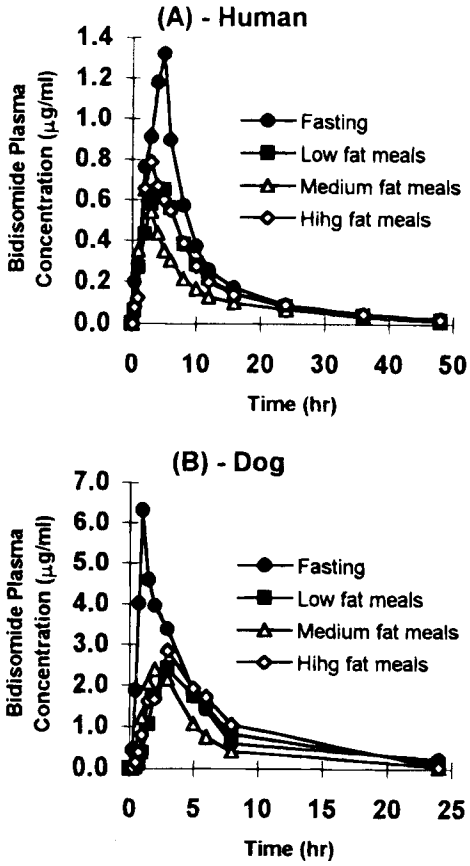

Fig. 1. Mean plasma concentration-time profiles of bidisomide after oral administration in fasting and co-administration with low, medium, and high fat meals in (A) normal healthy volunteers and (B) dogs.

Table II. Effect of Meal Composition on the Pharmacokinetics of IV and Oral Bidisomide in Normal Healthy Volunteers and Oral Bidisomide in Dogs

Type of meals	AUC (μg·hr/ml)	C_{max} (μ/ml)	T_{max} (hr)
Human-Oral Studies	(0–48hr)		
Fasting	10.97 ± 3.49	1.68 ± 0.64	3.88 ± 1.21
Low fat meal	7.57 ± 2.93*	0.79 ± 0.37*	4.25 ± 1.24
Medium fat meal	5.59 ± 2.41*	0.79 ± 0.47*	2.44 ± 1.31*
High fat meal	7.99 ± 3.20*	0.94 ± 0.43*	3.50 ± 1.31
Dog-Oral Studies	(0–8 hr)		
Fasting	19.7 ± 5.6	7.26 ± 2.46	3.88 ± 1.21
Low fat meal	11.3 ± 1.0*	2.59 ± 0.32*	4.25 ± 1.24
Medium fat meal	9.79 ± 2.9*	2.79 ± 0.66*	2.44 ± 1.31*
High fat meal	13.3 ± 5.9*	3.51 ± 1.48*	3.50 ± 1.31
Human-iv. Studies	(0–24 hr)		
Fasting	10.45 ± 1.46	4.75 ± 0.69	0.46 ± 0.07
High fat meal	9.02 ± 1.50*	4.51 ± 1.17	0.47 ± 0.04

*$p < 0.05$ as compared to fasting state.

were statistically significantly lower than AUC from bidisomide infusion in the fasted state in human subjects (Table II). However, this 13% reduction in AUC was not as dramatic as the 43% to 63% bidisomide plasma level AUC reduction observed in the oral bidisomide meal effect studies.

Drug Binding Studies with Meal Homogenate

The equilibration time of bidisomide in the control studies was approximately 4 hours. Based on these studies and projected gastrointestinal residence times, drug equilibration with cooked meal homogenates was determined at 4 and 6 hours by measuring drug concentration outside and inside the dialysis tubing at these time points. The percentage of bidisomide and disopyramide lost by binding to homogenates of cooked breakfast were 25.0 ± 5.7% and 23.7 ± 7.7% at 4 hours and 18.9 ± 4.8% and 18.4 ± 6.8% at 6 hours, respectively. The results indicated no statistically significant difference between the extent of drug loss for bidisomide and disopyramide at the time points selected.

Canine Meal Composition Studies

The bidisomide plasma level profiles for the fasted-state control and three meal treatments in dogs are provided in Figure 1(B). These profiles mirror those of the human meal composition study (Fig. 1(A)) in spite of the lower fasted state volumes (5 mL/kg) administered to dogs as compared to the human study (180 mL water). Again, both bidisomide plasma level C_{max} and AUC were significantly lower with co-administration of each of the meal treatments as compared to fasted-state control studies (Table II). The AUC was decreased 29.43%, 49.43%, and 39.7% after co-administration of bidisomide with high, medium, and low fat meals, respectively, as compared to fasted-state.

Absorption Site Study in Dogs

The extent of disopyramide absorption was similar for all three sites (Fig. 2(B)). The extent of bidisomide absorption was comparable from oral and duodenal administration while mid-jejunal administration provided significantly lower systemic drug availability (Fig. 2(A)).

Solid Versus Liquid Meal Studies

Since a liquid nutrient meal did not depress bidisomide AUC (Fig. 3) as was the case with previous solid meal co-administration in dogs (Fig. 1(B)), 250Kcal of a canned dog food (solid) was homogenized and orally co-administered with bidisomide. This meal did reduce bidisomide AUC in line with

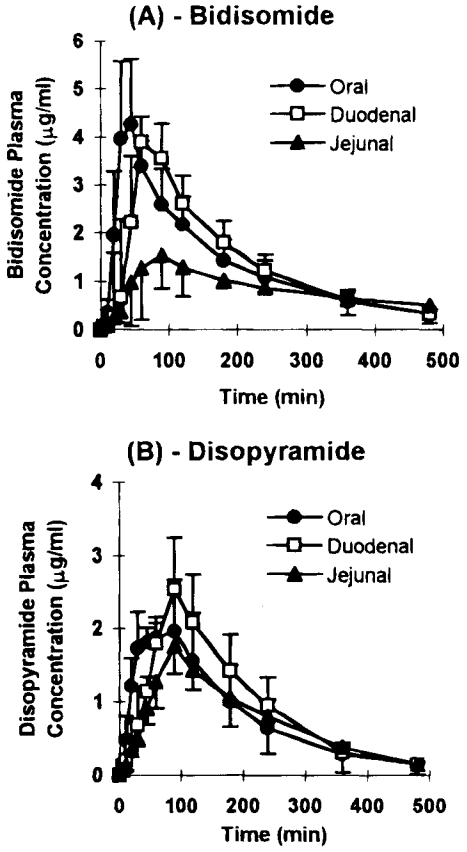

Fig. 2. Mean plasma concentration-time profiles of (A) bidisomide and (B) disopyramide following oral administration and 1 hr intestinal infusions at 3.82 ml/min in four dogs.

observations from previous studies using solid meal homogenates in dogs. A study in four dogs comparing oral bidisomide administration in water (control, n = 4) with oral co-administration of 250Kcal liquid enteral nutrient (Ensure®) and oral co-administration with 250Kcal homogenized solid dog food in three dogs, statistically confirmed that the liquid nutrient decreased bidisomide C_{max} only while the homogenized dog food decreased both plasma level C_{max} and AUC (Fig. 3).

Meal Viscosity Studies

Since a primary difference between the equivalent-calorie liquid meal and homogenized solid meal is medium viscosity, a calorie-free pH-independent viscosity-expanding agent (hydroxypropyl methylcellulose, HPMC) was utilized in an attempt to mimic the viscosity component of the meal effect on drug plasma levels. Shear rate versus shear stress profiles were measured to formulate a noncaloric meal with viscosity characteristics similar to the solid dog food homogenate (Fig. 4). Oral co-administration of this calorie-free HPMC formulation provided the same bidisomide plasma level profiles as was observed with the dog food homogenate (Fig. 5(A)) with a significant decrease in AUC as compared to fasted control animals. When this same study was carried out with disopyramide, the viscous meal delayed t_{max} but failed to alter AUC (Fig. 5(B)).

DISCUSSION

Equivalent bidisomide plasma level reductions were observed with high-, medium- and low-fat meals in both human and dog. Meal effects have not been observed to have a significant impact on disopyramide plasma levels in either species. While a high-fat meal did decrease the area under the bidisomide plasma level versus time curve by 13% when drug was intravenously administered, this reduction is substantially smaller than that observed when bidisomide is orally co-administered with meals. These results provided a rationalization for the utility of a canine model in the mechanistic studies carried out to isolate factors contributing to a negative food effect on bidisomide absorption.

Previous studies on site-specific intestinal absorption of bidisomide in man (4) and rat (6) prompted initial study in beagle dogs utilizing chronic intestinal access ports (10,11) to evaluate this large animal model for studying meal effects on drug absorption (12). In this study, the regional-dependent differences between the two drugs suggested that a meal-effected depression of drug availability for absorption in the upper small intestine could account for the negative meal effect observed with bidisomide.

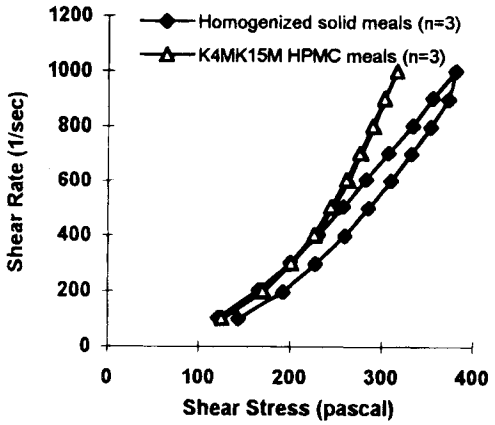

Fig. 4. Mean shear rate versus shear stress profiles of homogenized solid meals and K4MK15M HPMC meals.

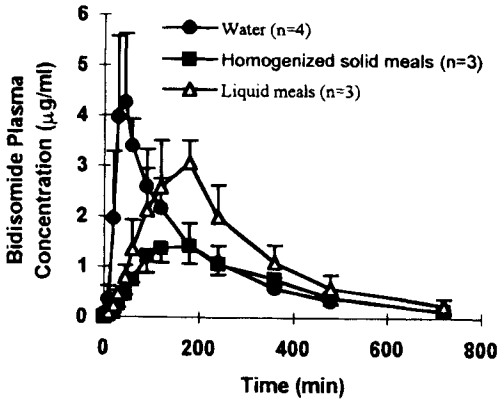

Fig. 3. Mean plasma concentration-time profiles of bidisomide following oral administration of bidisomide with water, Ensure® liquid nutrient, and homogenized solid nutrient in dogs.

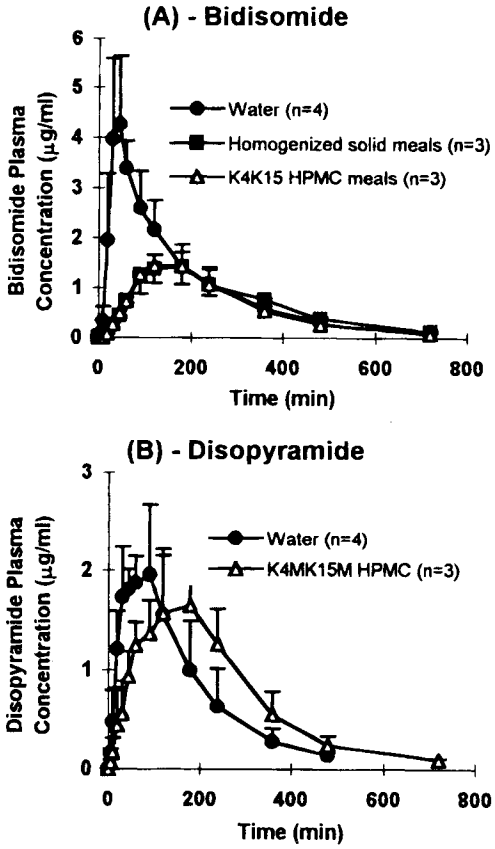

Fig. 5. Mean plasma concentration-time profiles of oral co-administration of (A) bidisomide with water, homogenized solid meals and K4MK15M HPMC meals and (B) disopyramide with water and K4MK15M HPMC meals in dogs.

This connection was made through the observation that equivalent calorie liquid meals did not reduce the extent of bidisomide absorption as compared to solid meal homogenates. We have previously utilized simple *liquid* nutrient sources to isolate specific fed-state contributions to drug absorption variability (13,14,15). In this study, liquid 250 Kcal meals (equivalent to the caloric load of the low fat meals in the dog and human meal composition studies) decreased C_{max} and increased t_{max} compared to aqueous bidisomide equivalent-pH, equivalent-volume controls but did not depress equal-dose bidisomide AUC. When this same quantity of calories was given as a homogenate of solid dog food, bidisomide AUC decreased consistent with the solid breakfast meal studies in dog and man. This result suggested caloric slowing of gastric emptying rate did not play a significant role in the observed negative food effect on bidisomide absorption since co-administration of bidisomide with meals only delayed but did not effect the extent of absorption. This is certainly the case at the high volume loads (200 mL) used in this study since the non-caloric load employed in the control study will empty rapidly (16).

Variable volume effects may complicate a food effect study. In the human and canine meal composition studies, initial volume loads varied between treatments. It is certainly possible, therefore, that bidisomide concentration driving forces for absorption differed between treatments. Even if initial volumes had been controlled, GI secretions and fluid absorption are a strong function of meal composition so volume, like pH and osmolality, cannot be maintained over the time course of a food effect study. Digestive factors will also serve to alter caloric density even if meal volume load is controlled initially. Thus both nutrient and drug concentration driving forces for absorption may vary with treatment subsequent to initial presentation.

The pK_as for bidisomide and disopyramide are 9.26 and 10.4, respectively. Since both drugs are weak bases with high pK_as, they are positively charged over the GI pH range and solubility or dissolution rate would not be projected to be rate-limiting to absorption. Furthermore, the ionized drug fraction available for absorption would not be appreciably changed as a function of GI region or input conditions. However, since the drugs are present in the lumen as charged species, a difference in their binding to meal components might result in a difference in meal effects. Equivalent loss of the two drugs to homogenized breakfast in dialysis studies reported here suggests that the food effect is not due to a physical interaction of bidisomide with food. A similarly equivalent binding result for these drugs was obtained with rat chow in a recent report examining the food effect on these drugs in rats (6). However, a stronger physical interaction between *digested* food components and bidisomide (as compared to disopyramide) could effect differences in fed-state absorption between these two drugs.

A major difference between the solid homogenate and liquid meals is medium viscosity. By mimicking the homogenized solid meal viscosity with a non-caloric HPMC formulation, a bidisomide plasma level profile could be obtained which mirrored that of the drug administration with the homogenized solid meal. This result suggests that the viscosity component of a meal could reduce bidisomide AUC independent of meal calorie composition. It is well recognized that dietary fibre alters the motility of the stomach and small intestine (17). Increasing the viscosity of the luminal contents may impair both fluid transit and diffusion of drug and nutrients in the intestine. The residence time (V/Q) for a drug in a specific intestinal region is a function of the fluid volume, V, and the intestinal flow rate, Q. Intestinal flow rate is an inverse function of lumenal medium viscosity (18) so increasing the lumenal viscosity should prolong upper intestinal residence time. The time for radial diffusion (r^2/D) of drug molecules over a distance from inside the intestinal lumen to the absorbing intestinal membrane, r, is a direct function of lumenal medium viscosity since the diffusion coefficient, D, is an inverse function of medium viscosity (19). Therefore, the time for drug diffusion to the absorbing membrane is increased with increasing lumenal viscosity. As the molecular size of both drugs is about the same, it is anticipated that the diffusion time would be equivalently increased for both drugs. Since the absorption site experiments indicate that bidisomide is well absorbed in the upper small intestine, meal viscosity should reduce the extent of absorption of bidisomide. These results suggest that the decrease in diffusivity through the meal homogenate may predominate over the increase in residence time leading to a decrease in absorption. This will not be as significant for disopyramide which appears to be well absorbed in both the upper and lower small intestine. This is consistent with studies in animals showing that upper intestinal contents are highly viscous following administration of a solid meal while digestion reduces viscosity substantially by mid-jejunum (17,20). These same studies have shown that the input viscosity of the HPMC meals is reduced by about 50% during passage through the upper gastrointestinal tract.

The reason for bidisomide's poorer lower intestinal absorption, as compared to that of the chemically-related disopyramide, is of significant interest. Recently, a number of drugs have been shown to be secreted back into the intestinal lumen following absorption (21). Bidisomide's site-dependent absorption might therefore be a function of site-specific intestinal clearance in rat, dog and man (4). This postulate is consistent with the observation that the extent of bidisomide absorption increases with increasing dose in man (3), dog (7) and rat (6) suggesting the possible saturation of an intestinal secretion mechanism.

It is essential to have information on the site- or region-dependent absorption of a drug to provide a rational basis for development of a controlled-release dosage form. However, little is known about local absorption characteristics along the gastrointestinal tract for most drugs (22). It is also well known that bioavailability of drugs can be influenced by food in the gastrointestinal tract, and such interactions have largely been addressed in a phenomenological manner (23). A mechanistic relationship between site-specific absorption and food effects on drug absorption has not been previously documented. In this study, the observation of a negative food effect for a drug with limited lower small intestinal absorption, suggest that meal viscosity may play a role. Food does not affect disopyramide absorption which offers a regionally-independent absorption profile. These results suggest that a drug candidate's regional absorption profile provides valuable information on the potential for a food effect. The possibility that the meal viscosity effect operates more generally for some drugs with an early t_{max} (indicating preferential absorption in the upper small intestine) is currently under study.

The bidisomide-disopyramide comparison has been useful to isolate one mechanism for a negative meal-effect on drug absorption. The utility of this information in evaluating food effects for other drugs will certainly be a function of the drug's absorption profile. That this effect might be more general would be enhanced by demonstrating a meal viscosity role for negative food effects on other drugs. Crixivan®, the HIV protease inhibitor, is absorbed predominantly in the upper small intestine in dogs (24), shows an early t_{max} (0.8 hrs) in humans, and meal co-administration reduces drug absorption (25). This drug is certainly a candidate for meal viscosity to negatively effect absorption.

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