Mechanisms of Food Effects of Structurally Related Antiarrhythmic Drugs, Disopyramide and Bidisomide in the Rat

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Purpose. To determine whether the rat is a good animal model for the food effects observed with bidisomide but not with the structurally similar antiarrhythmic drug, disopyramide in man and to explore a reason for the differences in the food effects of these compounds.
Methods. The following effects on the absorption of bidisomide and/or disopyramide were examined in the rat: Food effects, gastrointestinal transit time under fasting and nonfasting conditions, pH effects, hypertonic solution effect of NaCl and glucose, bile effects, permeability, inhibitory effects by Gly, Gly-Gly, Gly-Pro, glucose and mannitol and drug binding to food.
Results. Remarkable food effects were observed with bidisomide but not with disopyramide. There was no difference in the GI transit time with and without food. The pH effect with and without food was similar. Effect of salt concentrations on bidisomide and disopyramide was similar. There was no bile effect on absorption of both compounds. Binding of bidisomide and disopyramide to food was similarly low. The apparent permeability of bidisomide was much lower than disopyramide especially in the ileum and its absorption was more inhibited by Gly, Gly-Gly and Gly-Pro.
Conclusions. In the rat, as previously seen in humans, the food effect was observed with bidisomide but not with disopyramide. This difference was in part due to both lower intestinal permeability of bidisomide compared to disopyramide and greater inhibition of absorption by the amino acid, Gly and the dipeptides, Gly-Gly and Gly-Pro.

KEY WORDS: food effect; disopyramide; bidisomide; rat.

INTRODUCTION

Bidisomide (SC-40230), an antiarrhythmic agent is structurally similar to disopyramide (Fig 1). Disopyramide is widely used as a quinidine-like antiarrhythmic drug (1). Although these compounds are structurally similar, their absorption characteristics and food effects are remarkably different. Disopyramide is well absorbed in animals (2) and man (3). In contrast, absorption of bidisomide is complex in man, characterized by a lag period (0.75–1.5 h) before absorption, followed by occurrence of two peaks in plasma concentration-time curves (4,5). The systemic availability was 42–62% in man when the drug was administered orally after overnight fasting. However, the systemic availability of bidisomide in man was greatly reduced when administered with food (6). The systemic availability of disopyramide was not affected by food in man (7). Although there are many drugs whose bioavailability is influenced by food, there are very few investigations on the mechanism of those food effects. The present study was conducted to determine whether the rat is a good animal model for the food effects observed with bidisomide but not with disopyramide in man and also to explore possible mechanisms for the differences in the food effects of the structurally similar compounds.

MATERIALS AND METHODS

Materials

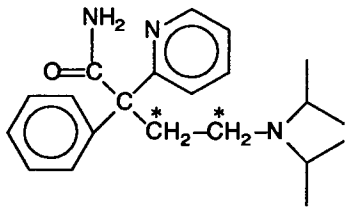
[^{14}C]Disopyramide (Lot No. GDS4361-19, specific activity of 41.1 μCi/mg), [^{14}C]bidisomide Lot No. GDS1840-170, specific activity of 24.0 μCi/mg), unlabeled disopyramide and bidisomide were obtained from G. D. Searle & Co. All other chemicals used were commercially available.

Animal Study

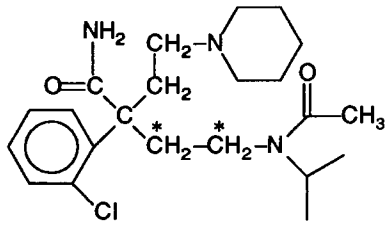
The animal studies were approved by the local committee of Laboratory Animal Care in accordance with the rules and guidelines. In all studies, male rats (CD strain) weighing 250–359 g were used. For in vivo studies oral doses of bidisomide and disopyramide were 25 and 15 mg/kg, respectively, and i.v. doses were 15 mg/kg for both compounds unless stated otherwise.

Food Effect

[^{14}C]Bidisomide or [^{14}C]disopyramide was administered to rats (N=4/group) with and without overnight fasting as either an oral solution or i.v. dose. Urine samples collected every 24 hrs for 48 hrs were analyzed for total radioactivity and the



Disopyramide



Bidisomide

Fig. 1. Chemical structure of [^{14}C]bidisomide and [^{14}C]disopyramide. Asterisks indicate the labeled carbon.

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parent drug using liquid scintillation counting (LSC) and HPLC procedures.

GI Transit Time

[^{14}C]Bidisomide was administered to the rat with and without overnight fasting. Four rats were sacrificed at specified time intervals and total radioactivity remaining in the gastrointestinal (GI) lumen and tissues was measured.

pH Effect

[^{14}C]Bidisomide (25 mg/kg) or [^{14}C]disopyramide (15 mg/kg) was administered orally to 4 male rats as 1M citrate (pH 4), 1M phosphate (pH 7) or 1M sodium carbonate (pH 10) buffer solution with and without overnight fasting. Urine samples were collected every 24 hrs for 48 hrs and analyzed for total radioactivity and parent drug.

Effect of Salt Concentration in Dose Solution

In order to examine the effects of salt concentration on absorption, [^{14}C]bidisomide or [^{14}C]disopyramide was directly introduced into the whole small intestine as NaCl (0, 0.15, 0.3 and 0.5 M) or glucose (0.15, 0.3, 0.5 and 1.0M) solution using the closed intestinal loop model (8). Blood samples were collected at various time points up to 2 hrs and plasma samples were analyzed for total radioactivity and the parent drug.

Bile Effect

[^{14}C]Bidisomide or [^{14}C]disopyramide was administered orally to the rat after overnight fasting as saline or rat bile solutions. The dose volume was 10 ml/kg regardless of the vehicle. Urine samples were collected for 48 hrs and analyzed for total radioactivity and the parent drug.

In Situ *Permeability*

An in situ study was conducted in the rat using a closed intestinal loop method in order to compare permeability of [^{14}C]bidisomide and [^{14}C]disopyramide. Small intestine and colon were gently washed with a saline solution (approx. 2.5 ml) to remove intestinal contents in the GI tract. Approximately 10 cm of jejunum, ileum and colon of each rat were ligated and a [^{14}C]bidisomide or [^{14}C]disopyramide solution (0.5 ml of 0.1 mg/ml or 2 mg/ml) was introduced. In addition, [^{3}H]PEG 4000 was added to determine leakage of the dosing solution from the loop. At 0, 0.5, 1 and 2 hrs following introduction of the drug solution, each ligated portion of the GI tract was separated and the mucosal layer was washed with saline (7–8 ml). Total radioactivity in the lumen and intestinal tissues was determined. The percentage of the dose absorbed was calculated as follows:

$$\% \text{ Dose Absorbed} = 100\% - (\% \text{ Dose Remaining in Lumen} + \% \text{ Dose Recovered in Tissue})$$

The percentages of the dose absorbed calculated using this equation was approximately the same as the values obtained from the drug concentrations which were normalized on the basis of [^{3}H]PEG 4000 concentrations in lumen. In each study, if the recovery of [^{3}H]PEG 4000 in GI lumen, mucosa and intestinal tissue combined was less than 90%, then the recovery values of the drugs were not used.

In Situ *Inhibition*

An in situ study for inhibition of [^{14}C]bidisomide and [^{14}C]disopyramide absorption was also conducted in the rat using the closed intestinal loop method. The dose solution (0.5 ml of 2 mg/ml) contained 0.75 M of Gly, Gly-Gly, Gly-Pro, glucose or mannitol in addition to carbon-14 drug and [^{3}H]PEG 4000. At 2 hrs following introduction of the drug solution containing an inhibitor to each segment of the GI tract, each ligated portion was separated and luminal fluid was collected. Total radioactivity in the lumen, mucosa and intestinal tissues was determined.

In Vitro Binding to Food

The pulverized rat chow was suspended in saline at a concentration of 200 mg/ml. [^{14}C]Bidisomide and [^{14}C]disopyramide were added at various concentrations and the mixture was shaken for 30 min. After centrifugation at 5000g, an aliquot of supernatant was counted for total radioactivity.

Sample Analysis

Plasma

Aliquots (100 μl) of each sample were mixed with 10 ml of Aquassure (Packard Instrument Co., CT) and the carbon-14 concentrations were determined by LSC. Plasma concentrations of [^{14}C]bidisomide and [^{14}C]disopyramide were determined by HPLC.

Urine and GI Fluid

Duplicate aliquots (50 μl) of each sample were mixed with 10 ml Aquassure and the concentrations of total radioactivity were determined by LSC. For determination of parent drug concentrations, selected samples were dried under a stream of nitrogen. The residue was reconstituted with 0.25 ml of the respective HPLC mobile phase and analyzed by HPLC.

GI Mucosa and Tissues

GI mucosa and tissues were dissolved using Soluene-350 (Packard Instrument Co.) for at least 24 hrs. The solubilized mucosa and tissues were mixed with 10 ml Aquassure and the concentrations of total radioactivity were determined by LSC.

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 in plasma and urine samples, a linear gradient system was employed from a solvent mixture of water: methanol:1M dibutylamine phosphate (DBAP) (94:5:1, by vol.) to a solvent mixture of acetonitrile: water: 1M DBAP (90:9:1, by vol.) over a 45 min period with

a flow rate of 1.4 ml/min. For plasma, urine and GI fluid samples of [^{14}C]disopyramide, an isocratic HPLC system was employed. The mobile phase was water: acetonitrile: methanol : 1M DBAP (70:19:10:1, by vol.) with a flow rate of 1.5 ml/min.

Plasma concentrations of [^{14}C]bidisomide and [^{14}C]disopyramide were determined using the ISCO Foxy fraction collector and LSC counting, and concentrations in urine and GI fluids were determined using a FLO-One detector (Flo-One/Beta Model IC or A250, Radiomatic Instruments and Chemical Co.).

Pharmacokinetic Model for Food Effect

Figure 2 shows a pharmacokinetic model in which drug and food interaction in the GI tract is depicted. In this model, the following assumptions were made for simplicity of the model: A movement rate constant (K_{20}) for the unbound drug and bound drug passing through the GI tract is the same. Food concentrations in the GI tract are much greater than the drug concentrations and binding of the drug is independent of food concentration. The absorption is first order and is not concentration dependent.

Amounts of D_3 in plasma in the presence ($[D_3]_F$) and in the absence ($[D_3]_{NF}$) of food can be given as follows:

$$[D_3]_F = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-K_{12}t} + De^{-K_{30}t} \quad (1)$$

where

$$A = \frac{K_{12}K_{23}\,D_0\,(K_{42} + K_{20} - \alpha)}{(\beta - \alpha)\,(K_{12} - \alpha)\,(K_{30} - \alpha)}$$

$$B = \frac{K_{12}K_{23}\,D_0\,(K_{42} + K_{20} - \beta)}{(\alpha - \beta)\,(K_{12} - \beta)\,(K_{30} - \beta)}$$

$$C = \frac{K_{12}K_{23}\,D_0\,(K_{42} + K_{20} - K_{12})}{(\alpha - K_{12})\,(\beta - K_{12})\,(K_{30} - K_{12})}$$

$$D = \frac{K_{12}K_{23}\,D_0\,(K_{42} + K_{20} - K_{30})}{(\alpha - K_{30})\,(\beta - K_{30})\,(K_{12} - K_{30})}$$

$$\alpha + \beta = 2K_{20} + K_{23} + K_{24} + K_{42}$$

$$\alpha\beta = K_{20}^2 + K_{20}K_{24} + K_{20}K_{23} + K_{20}K_{42} + K_{23}K_{42}$$

D_o = Initial dose

$$[D_3]_{NF} = Ee^{-K_{12}t} + Fe^{-(K_{20}+K_{23})t} + Ge^{-K_{30}t} \quad (2)$$

Where

$$E = \frac{K_{12}\,K_{23}\,D_0}{(K_{20} + K_{23} - K_{12})\,(K_{30} - K_{12})}$$

$$F = \frac{K_{12}\,K_{23}\,D_0}{(K_{12} - K_{20} - K_{23})\,(K_{30} - K_{20} - K_{23})}$$

$$G = \frac{K_{12}\,K_{23}\,D_0}{(K_{12} - K_{30})\,(K_{20} + K_{23} - K_{30})}$$

By direct integration of the differential equations, the area under the plasma concentration time curves with ($[AUC]_F$) and without ($[AUC]_{NF}$) food can be obtained as follows:

$$[AUC]_F = \frac{K_{23}\,(K_{20} + K_{42})\,D_0}{V[K_{30}\,(K_{20} + K_{23})\,(K_{20} + K_{42}) + K_{20}K_{24}K_{30}]} \quad (3)$$

$$[AUC]_{NF} = \frac{K_{23}\,D_0}{V \cdot K_{30}\,(K_{20} + K_{23})} \quad (4)$$

The ratio of

$$\frac{[AUC]_F}{[AUC]_{NF}} = \frac{(K_{20} + K_{23})(K_{20} + K_{42})}{(K_{20} + K_{23})\,(K_{20} + K_{42}) + K_{20}K_{24}} \quad (5)$$

As can be seen in Eq.5, a food effect ($[AUC]_F/[AUC]_{NF}$) is not only a function of binding constants with food (K_{24} and K_{42}) but also a function of permeability in the GI tract (K_{23}) and the elimination rate constant from the absorption site (K_{20}). Therefore, if two drugs have similar food binding characteristics and a similar window of absorption in the GI tract, the food effect will be greater for the compound with lower permeability (smaller K_{23}). This is shown graphically in Fig. 3. When K_{24} and K_{42} values are fixed, the smaller the K_{23} is, the more pronounced the food effect is for any given value of K_{20}. Over the ranges of K_{20} and K_{23} given, the maximum food effect due to differences in permeability is approximately a 30% reduction in $[AUC]_F$ with the ratio of $[AUC]_F/[AUC]_{NF}$ being 0.7.

RESULTS

Food Effect

After oral administration of [^{14}C]bidisomide to the rat without fasting, the percentages of the dose excreted as total radioactivity and the parent drug were remarkably reduced compared with those with fasting (Table I). In contrast to the oral dose, there was little food effect after i.v administration of [^{14}C]bidisomide. The ratio of the dose excreted as total radioactivity to the dose excreted as the parent drug in urine did not change with food, regardless of the dose route. These results indicate that food effect observed with bidisomide was not due to metabolism change with food but due to a reduction in absorption of bidisomide.

After oral and iv administration of [^{14}C]disopyramide, the percentages of the dose excreted in urine as total radioactivity and the parent drug in urine were not remarkably different with and without overnight fasting. As observed with bidisomide, the ratios of total radioactivity/parent drug in urine were approximately the same with and without fasting. Thus, the extent of both absorption and metabolism of disopyramide did not change notably when the drug was administered without overnight fasting as compared with overnight fasting.

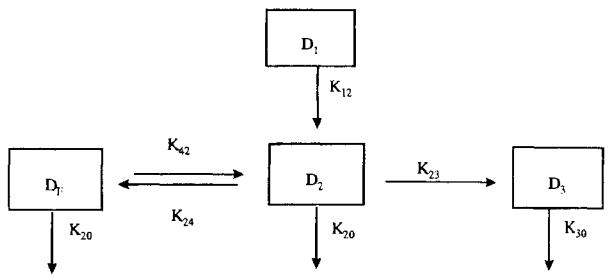

Fig. 2. Pharmacokinetic model for food effect. D_1 = Drug in the stomach, D_2 = Unbound drug in the GI tract, D_3 = Drug in blood, D_F = Drug bound to food.

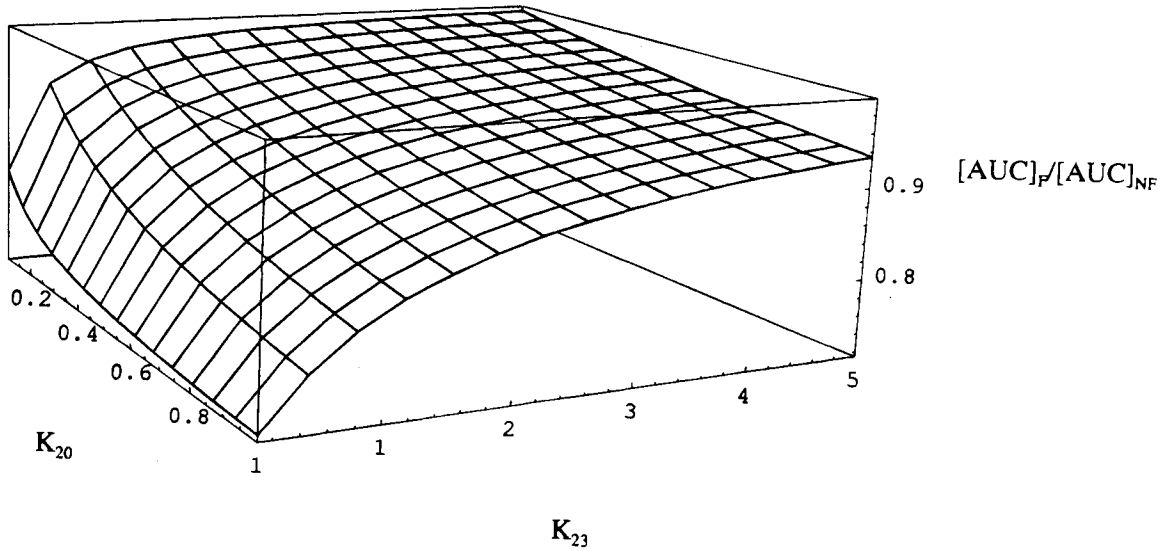

Fig. 3. Food effect ($[AUC]_F/[AUC]_{NF}$) calculated according to Eq. 5. K_{24} and K_{42} values were set to be 42 and 97 h^{-1}, respectively.

GI Transit Time

It has been reported that small intestinal transit is increased by administering a meal 30 min after dosing erythromycin (9), suggesting that the reduced residence time of a drug in the small intestine may result in reduced absorption. The GI transits of bidisomide in the rat were slightly different in the duodenum, jejunum and ileum with versus without overnight fasting (Fig. 4), despite the fact that rats do not feed during the day. After overnight fasting, the majority of [^{14}C]bidisomide was eliminated from the upper small intestine within 30 min and approximately 10% of the dose reached the lower portion of the small intestine. The maximal percentage of the radioactive drug in the lower portion of the small intestine was reached within 1 hr with fasting and substantial drug level (10% of the dose) was maintained for up to 3.5 hrs. Without fasting, substantial percentages of the administered dose did not reach the lower small intestine before 1 hr and maximal percentages of the administered dose in this region was achieved at 2.5 hrs. However, in the rat the time for [^{14}C]bidisomide to reach the colon was similar whether [^{14}C]bidisomide was administered with or without overnight fasting and no substantial percentages of the dose was recovered in the colon for up to 3 hrs. These findings, coupled with results from the intestinal permeability study, where there was no notable regional difference in bidisomide absorption, suggest that the food effect of bidisomide was not due to a change in the residence time of the drug at the absorption site. The percentages of the dose recovered in the colon was lower with fasting than without fasting. This is due to more absorption of bidisomide under fasting conditions.

pH Effect

When the pH of a dose solution was changed, more bidisomide was absorbed at pH 10 than at pH 4 and pH 7 with and without overnight fasting (Table II). However, the food effects of bidisomide were similar regardless of the pH of the dose solution. Disopyramide was absorbed more at pH 10 than at pH 4 and pH 7 after overnight fasting. As observed with the saline dose solution, no remakable food effect was evident at pHs 4 and 7. Thus, the food effect observed with bidisomide but not with disopyramide was not due to pH effects. Interestingly, with the pH 10 dose solution of disopyramide, the percent of dose excreted in urine was notably reduced under non-fasting conditions although there was no remarkable food effect when the drug was administered as pH 4 and pH 7 buffer solutions or as a saline solution (Tables I and II). One possibility for this is that water solubility of disopyramide free base at pH 10 is lower than that of its salts and available water volume for drug solution is reduced in the presence of food.

For both bidisomide and disopyramide, the percentages of the dose excreted as total radioactivity or the parent drug with

Table I. Mean (± S.D.) Percentages of the Dose Excreted as Total Radioactivity and Parent Drug in 0–48 hr Urine After Oral and IV Administration of [^{14}C]Bidisomide or [^{14}C]Disopyramide as a Saline Solution with and Without Overnight Fasting

Compound	Dose route	Fasting		Non-fasting	
		Carbon-14	Parent drug	Carbon-14	Parent drug
Bidisomide	Oral	21.0 ± 4.2	14.1 ± 2.4	7.8 ± 4.2	4.3 ± 2.2
	IV	63.7 ± 2.0	43.4 ± 2.2	66.0 ± 3.0	49.2 ± 1.8
Disopyramide	Oral	28.3 ± 3.0	18.4 ± 1.4	22.3 ± 3.6	14.2 ± 3.4
	IV	54.0 ± 3.8	40.1 ± 3.0	50.6 ± 3.2	36.2 ± 4.6

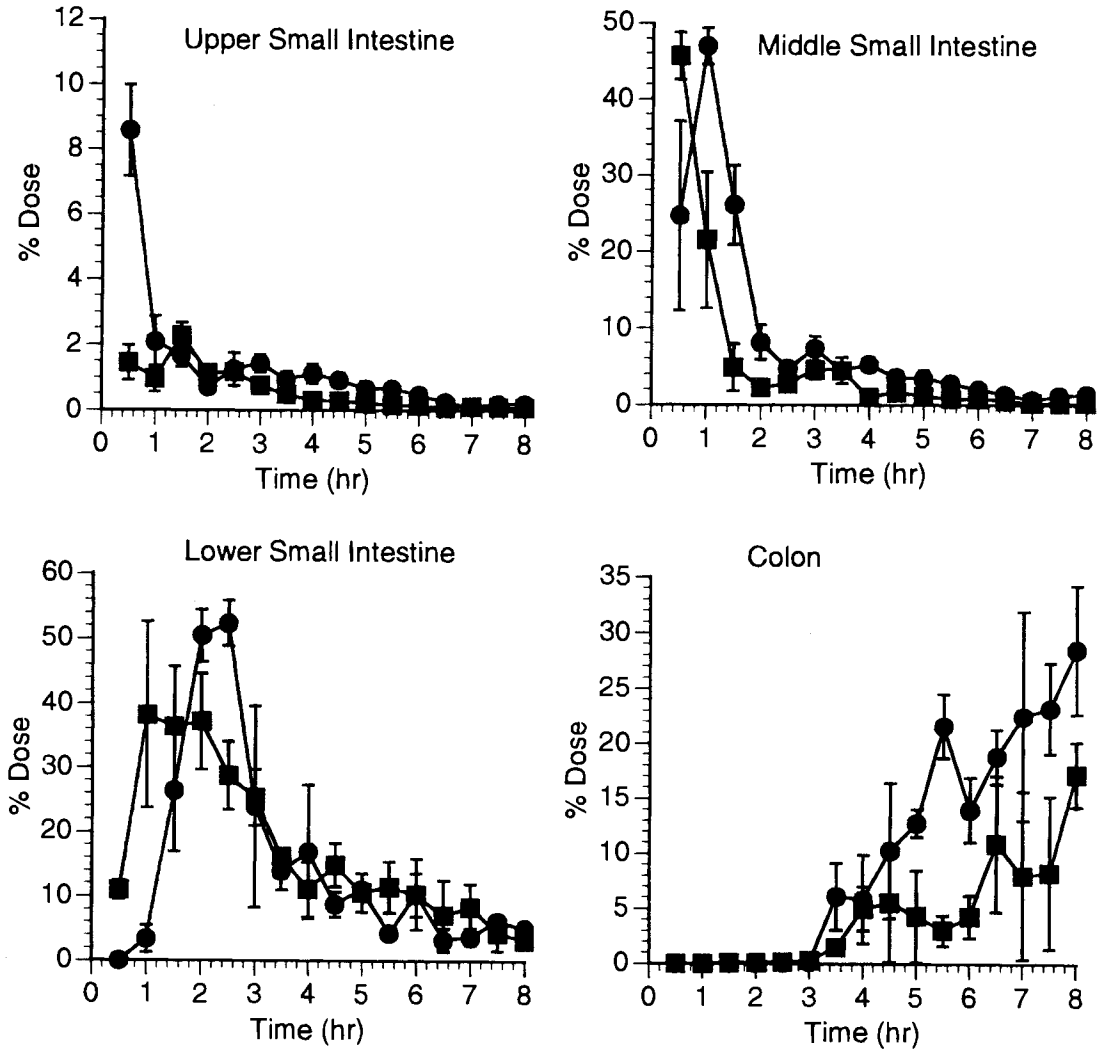

Fig. 4. Mean (± SE) percentages of the remaining dose in the various section of GI tract after oral administration of [^{14}C]bidisomide to the rat with (●) and without (■) overnight fasting.

a pH 10 buffer solution were similar to or lower than the values obtained with a saline dose solution. This appeared to be due to a high concentration (1M) of salt in the buffered dose solution as described below.

Effect of Salt Concentration in Dose Solution

In order to examine the effects of salt concentration in the dosing solution, [^{14}C]bidisomide and [^{14}C]disopyramide were administered by injecting directly into a closed loop of the whole small intestine as aqueous solutions of various salt concentrations. When [^{14}C]bidisomide was administered in a distilled water solution or in 0.15, 0.3 and 0.5 M NaCl solutions, the AUCs from 0 to 2 hrs in pooled plasma were 1.7, 1.1, 0.37 and 0.27 hr·μg/ml, respectively. The corresponding values for disopyramide were 1.9, 1.4, 0.53 and 0.24 hr·μg/ml, respectively. When [^{14}C]bidisomide was injected as glucose solutions

Table II. Mean (± S.D.) Percentages of the Dose Excreted as Total Radioactivity and Bidisomide in 0–48 hr Urine After Oral Administration of [^{14}C]Bidisomide as 1M Buffer Solutions of Different pH or as a Saline Solution

		Fasting		Non-fasting	
Compound	pH	Carbon-14	Parent drug	Carbon-14	Parent drug
Bidisomide	4.0	7.9 ± 2.0	4.8 ± 1.0	4.0 ± 1.0	2.1 ± 0.6
	7.0	6.18 ± 2.2	3.9 ± 1.2	2.8 ± 0.2	1.5 ± 0.2
	10	16.1 ± 1.6	9.8 ± 1.2	8.6 ± 3.4	4.6 ± 1.8
Disopyramide	4.0	9.9 ± 2.4	6.6 ± 0.7	11.1 ± 2.0	6.8 ± 0.7
	7.0	12.8 ± 5.6	6.8 ± 2.8	8.7 ± 2.5	4.7 ± 1.8
	10	20.9 ± 3.4	11.3 ± 1.0	12.4 ± 2.8	6.8 ± 1.4

at concentrations of 0.15, 0.3, 0.5 and 1.0 M, the AUC values were 2.3, 1.3, 0.94 and 0.55 hr·μg/ml, respectively. The corresponding values for disopyramide were 2.8, 2.3, 1.3 and 1.5 hr·μg/ml, respectively. Similar reduction of bidisomide and disopyramide AUC values with hypertonic dose solutions indicates that the difference in the food effects between the two drugs was not due to the hypertonic nature of the GI tract induced by food.

Bile Effect

After oral administration of [^{14}C]bidisomide to the fasted rats as saline or rat bile solutions, the mean percentages of the dose excreted as the parent drug in urine were 14.1 ± 1.0% and 12.9 ± 1.3%, respectively. After oral administration of [^{14}C]disopyramide, the corresponding values were 19.7 ± 1.9% and 22.4 ± 1.8%, respectively. These results indicate that the extent of bidisomide and disopyramide absorption did not change in bile solution. Therefore, enhancement of biliary excretion with food would not contribute substantially to the food effect of bidisomide observed in the rat.

Permeability

Absorption of bidisomide was concentration dependent, with more drug being absorbed at the higher concentration in the GI tract (Fig. 5). However, absorption of disopyramide which did not exhibit a discernable food effect was also concentration dependent in the same manner, indicating that concentration dependent absorption was not the reason why bidisomide absorption was reduced with food and disopyramide absorption was not.

Disopyramide was much more rapidly absorbed in all sections of the GI tract than bidisomide regardless of the dose. The extent of bidisomide absorption was similar in the jejunum, ileum and colon. The mean total recoveries of the drug at 2 hrs in the lumen, mucosa and tissues combined were 83.0–85.5% of the dose at the low dose and 57.6–62.1% at the high dose. In contrast to bidisomide, disopyramide absorption is much faster in the ileum than in the jejunum and colon, and 59.4% and 22.0% were recovered in the ileum at 1 and 2 hrs, respectively, at the low dose. Over the same time periods, only 16.3% and 10.4% were recovered in the ileum at the high dose.

Absorption Inhibition

Absorption of both bidisomide and disopyramide did not change significantly with Gly, Gly-Gly Gly-Pro and glucose in the jejunum, but decreased significantly ($p < 0.05$) with mannitol (Fig 6). However, in the ileum, absorption of bidisomide and disopyramide was significantly reduced, with all the compounds tested except for Gly inhibition of disopyramide (Fig. 6). The percentages of absorption inhibition by Gly, Gly-Gly, Gly-Pro, glucose and mannitol were 75%, 83%, 79%, 87% and 64%, respectively, for bidisomide and 19%, 58%, 48%, 78% and 80%, respectively, for disopyramide. These results indicate that the decrease in absorption with the amino acid and dipeptides was much greater with bidisomide than with disopyramide in the small intestine.

Absorption inhibition was more pronounced in the colon than in jejunum and ileum regardless of the inhibitor for both bidisomide and disopyramide. Since the inhibitors were poorly absorbed in the colon and the dose solution was highly hypertonic, there were notable increases in water volume in the colon, resulting in slight expansion of the colon. Therefore, pronounced regional difference in absorption inhibition may be due in part to the difference in absorption of inhibitors and back-flux of water into the intestine. This concept is supported by the fact that mannitol was not absorbed to a high extent in any sites of the GI tract and that there was notable expansion of the jejunum, ileum and colon. Furthermore, mannitol inhibited absorption of bidisomide and disopyramide nearly at all sites.

In Vitro Binding to Food

When [^{14}C]bidisomide and [^{14}C]disopyramide were added to pulverized rat chow suspension and the mixture was shaken for various time periods, the equilibrium of binding was reached within 2 min. The mean percentages of bidisomide binding to the food were 26.1 ± 0.1%, 20.0 ± 0.1% and 14.0 ± 0.3% at concentrations of 0.1, 10 and 50 mM, respectively. The corresponding values for disopyramide were 32.8 ± 0.7%, 27.9 ± 0.8% and 22.0 ± 0.7%, respectively. The similarly low percentages of bidisomide and disopyramide bound to food could not account for the remarkable food effects observed with bidisomide, but not with disopyramide.

DISCUSSION

Food effects on the bioavailability of drugs 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 (10–13). Consequently, the bioavailabilities of some drugs (e.g., propranolol, spironolactone) are enhanced with food whereas the bioavailabilities of other drugs are reduced (e.g., ampicillin, captopril) or unchanged (e.g., theophylline). Different formulations may also exhibit different food effects on the bioavailability for a given drug (13,14). The enhancement of biliary excretion by food increases solubility and dissolution of lipophilic drugs such as halofantrine (15) and propranolol (16). Furthermore, food increases the propranolol bioavailability by decreasing metabolism and increasing portal blood flow (17,18). The gastric pH increases during a meal whereas the duodenal pH decreases (19). These pH changes in the GI tract may also affect absorption of acidic or basic drugs.

The present study demonstrates that the remarkable difference in food effect between structurally similar compounds in the rat was at least in part due to differences in permeability through an intestinal wall and in the inhibitory effect of the amino acid and dipeptides. It was not due to the following factors: differences in drug binding to food, changes in the hypertonic nature of the GI tract induced by food, enhancement of biliary excretion with food, differences in GI transit time of the drug with and without food, pH changes in the GI tract, changes in the extent of metabolism, and concentration dependent absorption.

Permeability of disopyramide through the intestinal wall was much higher than that of bidisomide, especially in the ileum and approximately 70% of disopyramide was absorbed within the first 30 min. In contrast, only 12% of bidisomide was absorbed in the ileum over the same time period. The residence time of the drug in the ileum is longer than that in

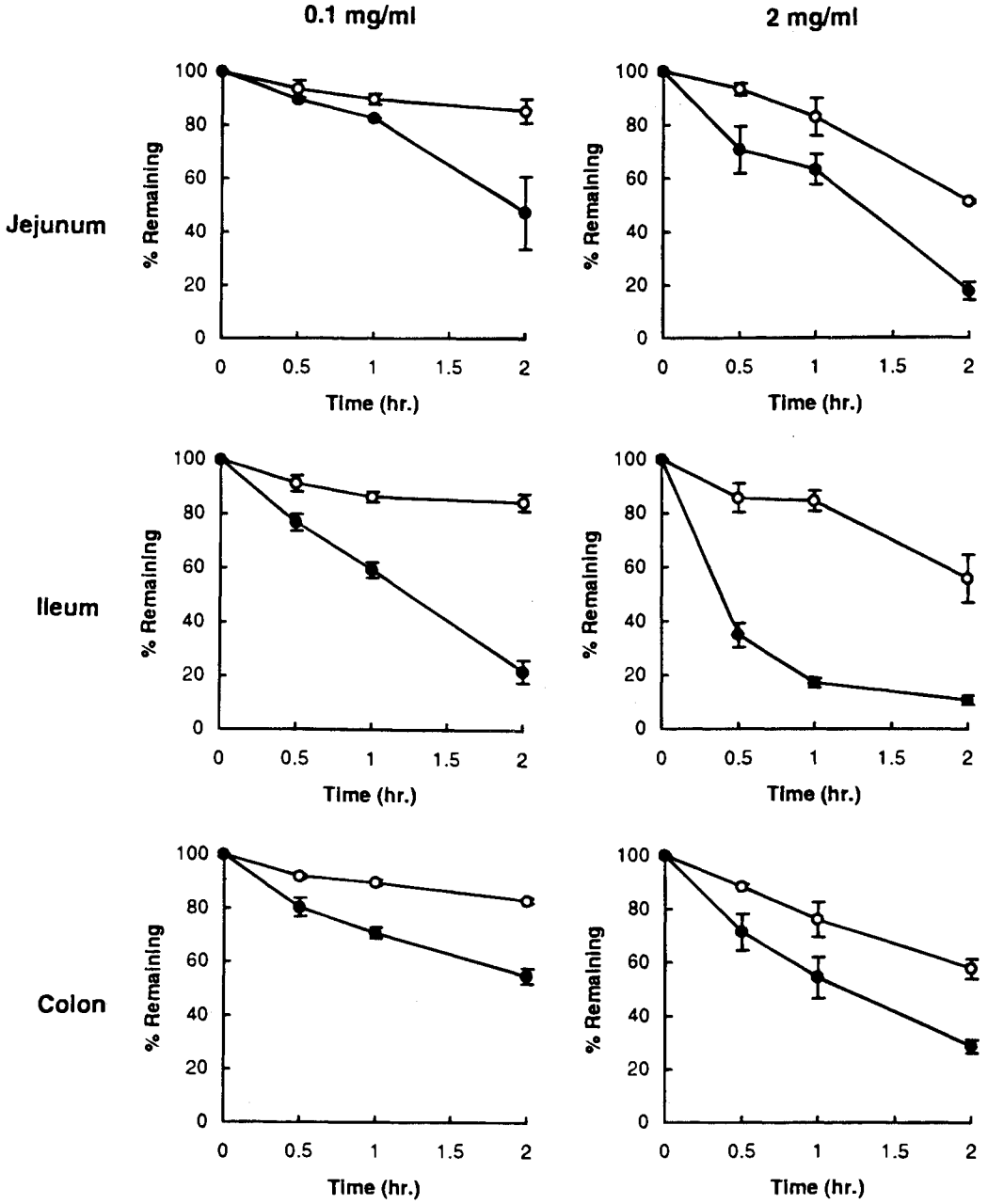

Fig. 5. Mean (± SE) percentages of the remaining dose after direct injection of [^{14}C]bidisomide (○) and [^{14}C]disopyramide (●) to the closed rat intestinal loop.

the jejunum or duodenum (Fig. 4). These results, together with high permeability in the ileum, indicate that the primary absorption site of disopyramide after oral administration is the ileum. Therefore, the food effect observed with bidisomide can be explained in part by the lower permeability of bidisomide in the GI tract as compared with disopyramide. This is conceivable because the binding of the drug to food is in an equilibrium state and the importance of food binding relative to absorption is dependent on the apparent absorption rate constant of a drug. This conception is further supported by the pharmacokinetic model proposed in the present report. In Eq. 5, it was demonstrated that the food effect is a function of the elimination rate constant from the absorption site (K_{20}), rate constants associated with food binding (K_{24} and K_{42}) and permeability (K_{23}). If K_{20}, K_{24} and K_{42} values of bidisomide are similar to those of disopyramide, then the food effect will be greater for bidisomide which has low K_{23} values.

In addition to permeability differences between bidisomide and disopyramide, there were also notable differences in the inhibitory effects of the amino acid, Gly and the dipeptides, Gly-Gly and Gly-Pro especially in the ileum. Absorption of disopyramide was not reduced significantly with Gly, whereas absorption of bidisomide was significantly reduced with this amino acid in the ileum (Fig. 6). With the dipeptides, Gly-Gly and Gly-Pro, absorption of bidisomide in the ileum was also reduced more as compared with disopyramide. Therefore, in

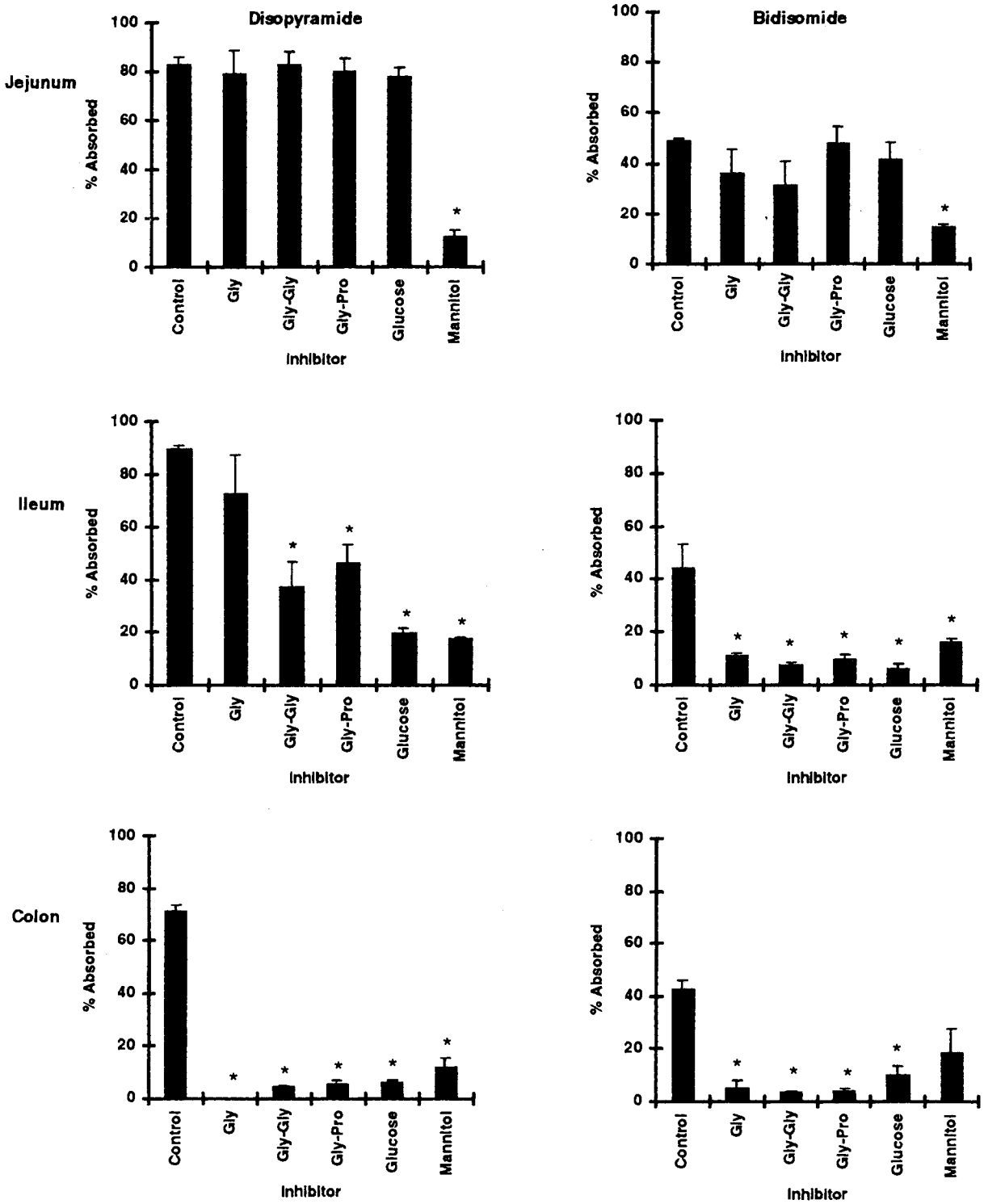

Fig. 6. Mean (± SE) percentages of the absorbed dose after direct injection of [^{14}C]bidisomide and [^{14}C]disopyramide to the closed rat intestinal loop with and without inhibitors. Asterisks indicate statistically significant ($p < 0.05$) difference between the control and treated groups.

the presence of food or digested food containing amino acids and dipeptides, bidisomide absorption is expected to be reduced more than disopyramide absorption. This will result in lowering the apparent K_{23} value for bidisomide more than that for disopyramide and subsequently result in more pronounced food effect for bidisomide. This is consistent with the food effects reported for other drugs, such as captopril (20), ampicillin (21) and dopamine (22) which have low permeability and are absorbed by the peptide or amino acid transport systems. However, the exact mechanism of inhibition of bidisomide and

disopyramide absorption by the amino acid and dipeptides is not known. These amino acid and dipeptides may directly inhibit the active transport systems and/or passive transport systems by enhancing back-flux of water into the intestine.

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