Pharmaceutical Research, Vol. 7, No. 3, 1990

Report

The Effect of Food on Gastrointestinal (GI) Transit of Sustained-Release Ibuprofen Tablets as Evaluated by Gamma Scintigraphy

Marie T. Borin,[1,2] Subhash Khare,[3] Robert M. Beihn,[3] and Michael Jay[3]

Received April 24, 1989; accepted October 10, 1989

The GI transit of radiolabeled sustained-release ibuprofen 800-mg tablets in eight healthy, fed volunteers was monitored using external gamma scintigraphy. Ibuprofen serum concentrations were determined from blood samples drawn over 36 hr following dosing. Sustained-release ibuprofen tablets containing 0.18% of $^{170}Er_2O_3$ (>96% ^{170}Er) in the bulk formulation were manufactured under pilot-scale conditions and were radiolabeled utilizing a neutron activation procedure which converted stable ^{170}Er to radioactive ^{171}Er ($t_{1/2}$ = 7.5 hr). At the time of dosing, each tablet contained 50 μCi of ^{171}Er. Dosage form position was reported at various time intervals. In five subjects the sustained-release tablet remained in the stomach and eroded slowly over 7–12 hr, resulting in gradual increases in small bowel radioactivity. In the remaining three subjects, the intact tablet was ejected from the stomach and a gastric residence time of approximately 4 hr was measured. This is in marked contrast to a previous study conducted in fasted volunteers in which gastric retention time ranged from 10 to 60 min. Differences in GI transit between fed and fasted volunteers had little effect on ibuprofen bioavailability. AUC and T_{max} were unaltered and C_{max} was increased by 24%, which is in agreement with results from a previous, crossover-design food effect study.

KEY WORDS: scintigraphy; neutron activation; bioavailability; ibuprofen; sustained release; food effect; gastrointestinal transit.

INTRODUCTION

The anatomical position of oral dosage forms in the GI tract can be monitored noninvasively *in vivo* using external gamma scintigraphic techniques. Gastric emptying and GI transit times of a variety of radiolabeled dosage forms have been monitored using this technique (1,2). Previous studies have evaluated enteric coated tablets in which a stable nuclide was incorporated into the dosage form with subsequent irradiation in a neutron flux, yielding a radiolabeled tablet (3,4). This dosage form was then administered to human volunteers and monitored with a gamma scintigraphy camera.

A recent study evaluated the transit of a sustained-release ibuprofen tablet through the GI tract (5). Tablets containing $^{170}Er_2O_3$ were irradiated, transforming the stable ^{170}Er into radioactive ^{171}Er. This radiolabeled dosage form was administered to fasted, healthy volunteers, and ibuprofen serum concentrations and related bioavailability parameters were correlated to the position of the tablet from scintiphotos. For ibuprofen, administration of a sustained-release tablet with a high-fat meal results in an increase in the rate of ibuprofen absorption, but the extent of absorption is unaltered (6). Administration of oral dosage forms with food, in particular high-fat meals, can result in delayed gastric emptying (7,8). For sustained-release oral dosage forms, administration with food can result in a failure of the dosage form to provide sustained drug levels (dose-dumping) (9,10). In the present study, external gamma scintigraphy was used to evaluate the GI transit characteristics of sustained-release ibuprofen tablets in fed volunteers and to correlate the position and integrity of the dosage form with pertinent bioavailability parameters.

MATERIALS AND METHODS

Sustained-release ibuprofen tablets containing 0.18% of $^{170}Er_2O_3$ (>96% ^{170}Er; Oak Ridge National Laboratories, Oak Ridge, Tennessee) were prepared and radiolabeled as described by Parr *et al.* (5). At the time of dosing, each tablet contained 50 μCi of ^{171}Er. Eight healthy, male volunteers (20 to 27 years of age) participated in the study following written informed consent and approval from the Institutional Review Board. The subjects were fasted overnight for 9.5 hr. One-half hour prior to dosing, each subject received a breakfast consisting of a McDonald biscuit with bacon, egg, and cheese, 8 oz of 2% fat milk, and one banana (750 kcal).

[1] Clinical Pharmacokinetics Unit, The Upjohn Company, 7000 Portage Road, Kalamazoo, Michigan 49001.
[2] To whom correspondence should be addressed.
[3] Division of Medicinal Chemistry, College of Pharmacy, University of Kentucky, Lexington, Kentucky 40536.

0724-8741/90/0300-0304$06.00/0

^{171}Er-Labeled sustained-release ibuprofen tablets were administered orally with 6 oz of water. Immediately after ingesting the tablet, each subject was positioned beneath the head of a gamma scintillation camera for 1 hr, during which a continuous dynamic scan was accumulated. After this time, subjects were permitted to ambulate freely (except during subsequent scanning). Static scintiphotos over 2–3 min were obtained at half-hour intervals. Scintigraphic data collected over the course of the study were recorded on a computer disk and replayed at a later time for detailed analysis. External markers placed on the subjects aided in determination of dosage form position in the GI tract.

Seven-milliliter blood samples were drawn via heparin lock at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, and 36 hr following tablet administration. Serum was harvested, immediately frozen, and kept in a frozen state until assayed for ibuprofen by HPLC (11).

RESULTS

The results of the scintigraphic portion of the study indicated that in five of eight subjects, the sustained-release tablet eroded in the stomach and pylorus. Thus, gastric emptying times for these volunteers were estimated from gastric emptying of radioactivity versus time plots, as well as visual observation of the partially eroded tablet remaining in the stomach. These values are given in Table I. Accordingly, it was not possible to determine small bowel and large bowel residence times as the activity in the small and large intestines increased gradually over time before the tablet left the stomach or completely eroded. In the remaining three subjects, the tablet remained relatively intact in the stomach prior to ejection into the small bowel. Scintigraphy data for these subjects are provided in Table II.

Mean ibuprofen serum concentrations for Subjects 1–5, in whom the tablet eroded while in the stomach, and Subjects 6–8, in whom the tablet was expelled from the stomach intact, are shown in Fig. 1. Average bioavailability parameters are given in Tables III and IV. C_{max} and T_{max} were obtained directly from individual subject serum concentration–time curves. Areas under the serum concentration–time curves from 0 to 36 hr [AUC(0–36)] and 0 to T_c [AUC(0–T_c)], where T_c is time to cecum, were calculated using the trapezoidal rule. AUC(0–T_c) values were estimated only for Subjects 6–8 since in the remaining subjects the tablet had eroded prior to reaching the cecum. AUC(0–∞) was not determined from these data since estimates of the terminal elimination rate constant could not be obtained due to prolonged absorption. However, in all subjects the concentration at 36 hr was below detection (<1 μg/ml) and thus, AUC(0–36) was a good estimate of the total extent of ibuprofen absorption.

Table I. Residence Times for Sustained-Release Ibuprofen Tablets in Subjects 1–5[a]

Subject No.	Gastric emptying time (hr)
1	11
2	12
3	9
4	11
5	12
Mean	11.0
SD	1.2
CV (%)	11.1

[a] Tablet eroded slowly in stomach/pylorus; estimated gastric emptying time represents time by which all activity had been emptied.

Table II. Residence and Transit Times for Sustained-Release Ibuprofen Tablets in Subjects 6–8[a]

Subject No.	Gastric emptying time (hr)	Small bowel residence time (hr)	Time to cecum (hr)
6	3.3	4.7	8
7	3.8	4.2	8
8	4.0	4.0	8
Mean	3.7	4.3	8
SD	0.36	0.36	0
CV (%)	9.7	8.4	0

[a] Intact tablet ejected from stomach.

In the "fast" gastric emptying group (Subjects 6–8), serum concentrations for the first 3 hr after dosing were lower than in the "slow" gastric emptying group (Subjects 1–5), as was C_{max} (17% lower), suggesting slower absorption. Although mean AUC(0–36) was lower in Subjects 6–8, this estimate was biased due to the low AUC(0–36) observed for Subject 8. Overall, there was no apparent difference in the extent of ibuprofen absorption between the two groups of subjects.

Ratios of AUC(0–T_c) to AUC(0–36) were estimated for Subjects 6–8 (Table IV). In Subject 8 the tablet was defecated after 12 hr. The AUC(0–36) for this subject was only 123 μg · hr/ml relative to values ranging from 183 to 247 μg · hr/ml for the other subjects, resulting in a high AUC(0–T_c)/AUC(0–36) relative to those for Subjects 6 and 7. Defecation of the dosage form prior to complete erosion and drug release was also noted by Parr *et al.* in one fasted volunteer (5).

DISCUSSION

Comparisons between the results of this study in fed volunteers and those of a previous study in fasted volunteers utilizing the same radiolabeled sustained-release tablets revealed several important differences in tablet erosion and GI

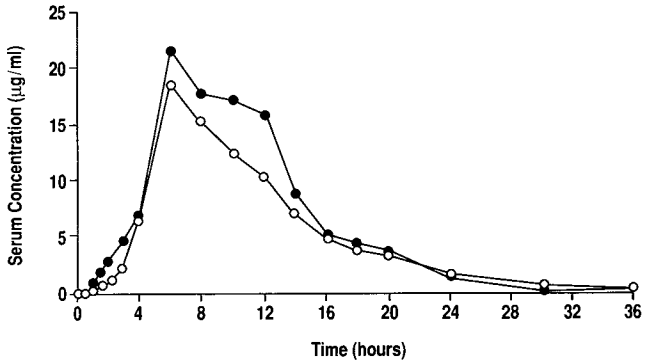

Fig. 1. Average ibuprofen serum concentrations versus time plots for Subjects 1–5 (●) and Subjects 6–8 (○).

Table III. Average Bioavailability Parameters for Subjects 1–5[a]

Subject No.	C_{max} (μg/ml)	T_{max} (hr)	AUC (0–36) (μg · hr/ml)
1	17.3	8	205
2	21.0	8	247
3	30.0	6	234
4	22.2	6	183
5	21.5	6	200
Mean	22.4	6.8	213.8
SD	4.7	1.1	26.1
CV (%)	20.8	16.1	12.2

[a] Tablet eroded slowly in stomach/pylorus.

transit characteristics. When administered to fed volunteers, either the tablets resided in the stomach for an average of 11 hr and eroded in the stomach or an intact tablet was expelled from the stomach within 4 hr of dosing. Intersubject variability in gastric emptying of solid dosage forms has been observed to be much greater in fed than fasted volunteers in other studies we have conducted (unpublished data). Although the rate of gastric emptying depends primarily on the caloric content of the ingested meal, other factors, such as GI physiology and body posture, exercise, and emotional state, can also influence gastric emptying (12). In fasted volunteers, the tablet emptied from the stomach in less than 1 hr and remained relatively intact upon reaching the cecum. Thus, the presence of food in the stomach resulted in delayed gastric emptying of the sustained release tablet, as expected. However, this did not result in a significant alteration in the drug's bioavailability. Mean C_{max} and T_{max} values were 24% higher and 13% lower, respectively, for fed versus fasted subjects. This finding is consistent with a previous report in which an increase in the rate of ibuprofen absorption was noted following administration of sustained-release tablets to fed volunteers (6). Food-induced increases in the rate of absorption of other drugs, most notably theophylline, have also been reported with controlled-release products (9,10,12–14). The mechanism for such an absorption change is unknown but thought to be due to increased secretion of bile, pancreatic fluid, digestive enzymes, and gastric hormones which occurs following high-fat meals. Although there was a 10% difference in AUC between the fed and the fasted groups, this is most likely due to differences in drug sampling times, which resulted in an AUC(0–24) being compared with an AUC(0–36) in the present study. Results of a crossover-design bioavailability study have shown that the extent of ibuprofen absorption is unaffected by administration of this sustained-release ibuprofen tablet with food (6).

For this particular dosage form, double peaks have been observed when the drug has been administered in the fasted state (5; unpublished data). Parr *et al.* attributed this to a loss of integrity of the dosage form in the large bowel which occurred coincident with the second peak (10–12 hr). This second peak was also observed in six of eight of the fed subjects at the same time as in fasted volunteers. Occurrence of the second peak in the fed subjects was unrelated to gastric emptying rate since this peak was observed in all but one subject in each of the "fast" or "slow" gastric emptying groups, suggesting that erosion and breakup of the tablet were independent of pH and location in the GI tract. This phenomenon could also be due to an increase in drug permeability in the colon.

Administration of radiolabeled sustained-release ibuprofen tablets with food allowed for monitoring of the tablet's position in the GI tract over time. The gastric emptying times for fed volunteers were considerably longer than for fasted volunteers (3.3 to 12 hr versus 10 to 60 min). Because of this, the dosage form eroded and began to break up in the stomach in several of the fed subjects. However, differences in tablet position in the GI tract over time did not result in substantial alterations in bioavailability parameters, further supporting the hypothesis that ibuprofen is well absorbed throughout the GI tract. Because of the variability in GI transit under fed conditions, this sustained-release erodible matrix system may not be a good choice for compounds which exhibit site specific drug absorption (absorption windows).

Although comparisons of pharmacokinetic data alone are sufficient in assessing the effect of food on drug bioavailability, knowledge of dosage form position correlated with bioavailability is a useful tool for studying sustained-release dosage forms from a developmental and therapeutic perspective. The results of the present study indicated that erosion of this particular sustained-release matrix tablet was a time-dependent phenomenon and was independent of dosage form location and pH.

ACKNOWLEDGMENTS

The authors wish to thank Ms. Susan Yonts for scintigraphic imaging of the subjects, Dr. Y. Ryo for medical supervision, and Ms. Sheila O'Meara for typing the manuscript.

Table IV. Average Bioavailability Parameters for Subjects 6–8[a]

Subject No.	C_{max} (μg/ml)	T_{max} (hr)	AUC(0–T_c) (μg · hr/ml)	AUC(0–36) (μg · hr/ml)	[AUC(0–T_c)/AUC(0–36)] × 100%
6	18.9	6	64.5	191	33.8
7	17.3	6	64.8	209	31.0
8	19.4	6	65.4	123	53.1
Mean	18.5	6	64.9	174.3	39.3
SD	1.1	0	0.5	45.4	12.0
CV (%)	5.9	0	0.71	26.0	30.6

[a] Intact tablet ejected from stomach.

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