Absorption of Flurbiprofen in the Fed and Fasted States

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The oral absorption of flurbiprofen, an antiinflammatory nonsteroidal compound, was compared in the fasted vs the fed state. When ingested as an aqueous solution of the sodium salt, absorption kinetics followed a monoexponential pattern in half of the subjects and a bimodal pattern with a lag time before the onset of the second phase of absorption in the other half of the subjects. When ingested in the free acid form as a tablet either with water (fasted state) or with water 15 min after 330 ml of apple juice (fed state), flurbiprofen absorption was always bimodal, and the lag time before the onset of the second phase was shown to be dependent on the gastric emptying time ($r = 0.623$, $P < 0.01$). The gastric emptying times were significantly longer when the drug was administered in the fed state (average GET = 57 min in the fasted state and 102 min in the fed state; $P < 0.01$). These results suggest that gastric emptying effects are one important way in which absorption of drugs can be affected by meal intake.

KEY WORDS: flurbiprofen; oral absorption; fasted state; fed state; gastric emptying.

INTRODUCTION

Absorption of most nonsteroidal antiinflammatory drugs (NSAIDs) appears to be delayed by food (1). Ibuprofen, for example, exhibits delayed absorption when given with food, although the area under the serum level vs time curve (AUC) is unaffected. It has been speculated that changes in the gastric emptying pattern are a major contributor to delays in the absorption of NSAIDs when they are administered with meals. However, previous studies which compared fed- vs fasted-state absorption of NSAIDs utilized multicomponent meals, making it difficult to discern the means by which the absorption profile was altered.

In the current study, we examined the effect of coadministration of a simple liquid "meal" on the absorption profile of flurbiprofen (Ansaid®, Upjohn), an analogue of ibuprofen, from an immediate-release solid dosage form. Specifically, we hypothesized that the difference in gastric emptying between the fed and the fasted state would result in a change in the absorption profile of flurbiprofen from the tablet dosage form.

Flurbiprofen was chosen for this study because it is lipophilic (partition coefficient of 10,417 between octanol and water), and it is known to be rapidly absorbed from solution (2), indicating that the intestinal permeability is high and unlikely to limit the absorption rate of flurbiprofen from solution. Furthermore, it is rapidly soluble at intestinal pH ($pK_a = 4.22$, solubility at pH 6 = 0.4 mg/ml), suggesting that dissolution from a conventional solid dosage form would not be rate limiting to absorption. Finally, it is a close structural analogue of ibuprofen, which has been shown to exhibit delayed absorption when coadministered with meals.

Apple juice was chosen as the "meal" so that effects related to meal-induced changes in the gastric emptying rate could be studied selectively. Since the pH of apple juice is 3.5, administration of apple juice minimizes changes in gastric pH and, therefore, in the dissolution rate of flurbiprofen. A calorie-dense liquid meal was chosen to induce normal feedback inhibition of the gastric emptying rate (3). By eliminating solids from the meal, we hoped to minimize the possibility of flurbiprofen adsorption or complexation with meal components. Any effects of an apple juice meal on the absorption profile of flurbiprofen would thus be expected to be associated primarily with a reduction in the emptying rate of the gastric contents.

METHODS

Subjects

Twelve healthy nonobese males aged 20 to 29 years participated in the study, which was approved by the Institutional Review Committee for Studies in Human Subjects at the University of Michigan. Exclusion criteria included a history of upper gastrointestinal, cardiac, pulmonary, renal, or hepatic disease, diabetes, allergies/hypersensitivity to NSAIDS, or difficulty in swallowing. To verify health status, each subject was evaluated by medical history, physical examination, and routine laboratory screens. For 30 days prior to and during the study, no enzyme inducing agents were permitted. All other medications were stopped 7 days before and throughout each study phase. Tobacco, caffeine, and alcohol were not permitted for 24 hr prior to and throughout each treatment phase, and strenuous exercise was prohibited on study days.

Study Design

The study was conducted at the Clinical Research Center of the University of Michigan Hospitals according to a randomized crossover design. Twelve subjects received each of the three treatments described below.

(i) Treatment A consisted of one flurbiprofen (free acid form) tablet, 100 mg, administered orally with 180 ml water.

(ii) Treatment B consisted of one flurbiprofen (free acid form) tablet, 100 mg, administered orally with 180

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ml water 15 min after the ingestion of 330 ml apple juice.

(iii) Treatment C consisted of 40 ml flurbiprofen oral solution (sodium salt, equivalent to 2.5 mg/ml of the free acid form) administered orally with 140 ml water.

In Treatments A and B subjects swallowed a Heidelberg capsule 30 min before administration of the flurbiprofen (Treatment A) or apple juice (Treatment B) to determine the effect of the fluid administered on the gastric emptying time. Treatment C was included so that accurate pharmacokinetic parameters could be calculated for distribution and elimination, thereby facilitating model construction for the absorption of flurbiprofen in Treatments A and B. Treatments were separated by at least 6 days for each subject.

Subjects fasted from 8 PM on the evening prior to each study day until 4 hr after flurbiprofen administration. During this time water was the only fluid permitted, with the exception of the apple juice given in Treatment B. In Treatments A and B, gastrointestinal (GI) pH was monitored until 1 hr after gastric emptying of the Heidelberg capsule occurred, or a maximum of 4 hr after flurbiprofen administration. The Heidelberg capsule was then retrieved orally and checked for agreement of pH measurements with prestudy calibration values, using standard buffer solutions.

During each study phase, 5-ml blood samples were drawn at the following intervals: prestudy (0.00), 0.17, 0.33, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10, 12, 24, 36, and 48 hr. For the first 12 hr of the study blood was collected through an indwelling catheter placed in the forearm, while at longer times individual venipunctures were used to collect samples. In all cases, 5-ml samples were collected (after a 3-ml discard volume in the case of catheter draws) in red-top Vacutainers (Vacutainer Systems, Rutherford, NJ) containing no preservatives. Serum was harvested from blood samples and immediately frozen at −20°C. All samples were analyzed by Hazleton Laboratories (Madison, WI) using a validated HPLC assay.

Use of the Heidelberg Capsule to Monitor Gastric Emptying

The Heidelberg capsule has been shown to measure GI pH accurately (4,5) and to be useful for detecting gastric emptying (6). Indigestible solids the size of the Heidelberg capsule are emptied from the stomach when an interdigestive migrating motor complex (IMMC) passes through the upper GI tract. The IMMC occurs in a cyclic fashion in the fasted state but is absent in the fed state. Emptying of the capsule is detected by a rapid, sustained rise in the pH, combined with an increase in the tether length. Specifically, a pH recording of greater than 5 for at least 1 hr following the initial rapid rise can be correlated with emptying of the capsule from the stomach to the duodenum (7). Supporting evidence for gastric emptying is provided by a concomitant increase in the tether length from 50–55 cm, typical of a gastric corpus location, to 70–80 cm, typical of a midduodenal location. In our study, the capsule position was monitored by observing the GI pH and the length of tether swallowed as a function of time. The capsule was tethered with a surgical thread marked at 10-cm intervals to facilitate the procedure.

An advantage of the Heidelberg capsule technique is that it is a relatively noninvasive method of monitoring gastric emptying. A disadvantage is that it reflects only the occurrence of an IMMC and is not sensitive to episodes of submaximal contractile activity, which may result in partial emptying of liquids and small solid particles (e.g., disintegrated tablets) from the stomach.

Validation of Apple Juice Effect on Gastric Emptying

Two healthy subjects, one 32-year-old female and one 35-year-old male, participated in the validation study. On Day 1, each subject received 300 ml of water, radiolabeled with ^{99m}Tc-DPTA, 0.5 mCi. On Day 2, each subject received 300 ml apple juice, similarly labeled. At least 1 week separated the 2 study days. On each occasion, gastric emptying of the ^{99m}Tc was followed continuously by gamma scintigraphy.

Data Analysis

In six subjects the oral solution data were best fitted using a two-compartment open model with one first-order absorption rate constant (Model I, Fig. 1) using RSTRIP (Micromath, P.O. Box 21550, Salt Lake City, UT). The concentration as a function of time according to Model I is given by

$$C_p = \frac{k_a D}{V_p}\left[\frac{(k_{21}-\lambda_1)e^{-\lambda_1 t}}{(k_a-\lambda_1)(\lambda_2-\lambda_1)} + \frac{(k_{21}-\lambda_2)e^{-\lambda_2 t}}{(k_a-\lambda_2)(\lambda_1-\lambda_2)} + \frac{(k_{21}-k_a)e^{-k_a t}}{(\lambda_1-k_a)(\lambda_2-k_a)}\right] \quad (1)$$

In the remaining six subjects the data were best fitted by a two-compartment open model with two first order absorption rate constants (Model II, Fig. 1) using MINSQ (Micromath). Model II assumes that initially there is only one rate constant governing absorption but that, at some later time, a second rate constant begins to contribute. The time at which

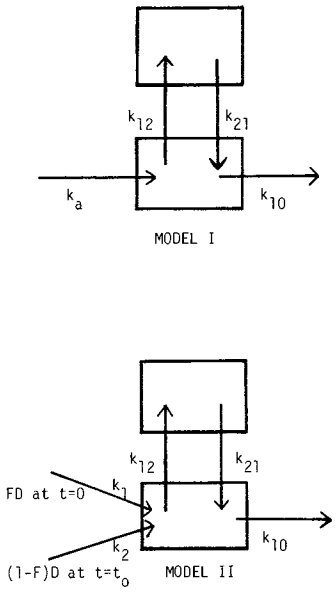

Fig. 1. Models for flurbiprofen kinetics after oral dosing.

the second rate constant begins to contribute is designated the lag time. Models of this type have been used previously to fit data for the absorption of penicillamine (8) and veralipride (9), among others. There are two equations governing the concentration vs time profile for Model II. During the lag time prior to the onset of absorption via the second rate constant, the concentration/time profile is given by Eq. (1), with k_1 replacing k_a and with F, the fraction of dose absorbed, being a multiplier for the whole equation. After the lag time ($t > t_o$), both absorption rate constants contribute to the concentration of flurbiprofen in the serum, and the concentration profile is given by

$$C_p = \frac{k_1 FD}{V_p}\left[\frac{(k_{21} - \lambda_1)e^{-\lambda_1 t}}{(k_1 - \lambda_1)(\lambda_2 - \lambda_1)} + \frac{(k_{21} - \lambda_2)e^{-\lambda_2 t}}{(k_1 - \lambda_2)(\lambda_1 - \lambda_2)} + \frac{(k_{21} - k_1)e^{-k_1 t}}{(\lambda_1 - k_1)(\lambda_2 - k_1)}\right] + \frac{k_2(1 - F)D}{V_p}\left[\frac{(k_{21} - \lambda_1)e^{-\lambda_1(t-t_0)}}{(k_2 - \lambda_1)(\lambda_2 - \lambda_1)} + \frac{(k_{21} - \lambda_2)e^{-\lambda_2(t-t_0)}}{(k_2 - \lambda_2)(\lambda_1 - \lambda_2)} + \frac{(k_{21} - k_2)e^{-k_2(t-t_0)}}{(\lambda_1 - k_2)(\lambda_2 - k_2)}\right] \quad (2)$$

Note that in Eq. (2), V_p is actually (V_p/fraction of dose absorbed) and F is the fraction of the absorbed dose that is absorbed according to k_1, while ($1 - F$) represents the fraction of the absorbed dose that is absorbed according to k_2.

Serum level vs time curves following administration of the tablet in either the fasted or the fed state all conformed to Model II. Goodness of fit was assessed by correlation coefficients and MSC (10) for both solution and tablet data.

Since flurbiprofen exhibits two-compartment characteristics, the exact Loo–Riegelman method was applied to estimate the fraction of drug absorbed as a function of time. The fraction of drug absorbed (FA) versus time data for each subject in Treatments A and B was obtained according to equations appropriate for Model II.

Paired t tests were used to test for significant differences between Treatment A and Treatment B for gastric emptying times of the Heidelberg capsules and for lag times. The correlation between gastric emptying time of the Heidelberg capsule and t_o (the lag time) was determined by applying a function of the form $y = bx$ to the data, then performing regression analysis using the MINSQ program.

RESULTS

Effect of Apple Juice on Gastric Emptying Rate

In the scintigraphy studies, the half-life for gastric emptying of water was 8.2 min in subject 1 and 16 min in subject 2. The half-life was extended to 16 min in subject 1 and 45 min in subject 2 when apple juice was administered. These studies were in accordance with earlier published data of Brener *et al.* (3), who found that glucose significantly decreases the rate of gastric emptying and that the degree of reduction depends on the caloric density of the fluid. From these results it appeared that an 11-oz drink of apple juice would provide a significant prolongation of gastric emptying time compared with a similar volume of water, provided that a paired-data trial design was used.

Oral Solution Data

Oral solution data exhibited a single peak in the serum level vs time profile in 4 of the 12 subjects, while in the remaining eight subjects double-peak, or shouldering, behavior was observed. Absorption from the oral solution was rapid, with a peak serum concentration occurring within 30 min of flurbiprofen administration in all subjects. A representative profile using data from subject 11 is shown in Fig. 2.

Absorption rate constants were rapid, with a mean of 9.97 hr^{-1} in the six subjects whose data conformed to Model I and a mean of 20.8 hr^{-1} for the second absorption rate constant in the six subjects whose data conformed to Model II.

Tablet Data

Double peaks or shoulders in the serum profiles were less evident after tablet administration than in the solution phase, with four subjects exhibiting this behavior in Treatment A and three in Treatment B. Model II gave satisfactory fits to the data in all cases except Subject 5, Treatment B. Data from this subject exhibited pronounced double-peak behavior, and the data were not included in further analyses due to poorness of fit.

Figure 3 shows the fraction absorbed vs time plots using the exact Loo–Riegelman method from subject 7. Calculated absorption rate constants, lag times, and fraction of absorbed drug that was absorbed via the k_1 pathway (F) are given for each subject in Tables I and II. The absorption rate constants were consistently lower when tablets were administered than when flurbiprofen was given in solution form. Furthermore, the k_1 values were lower in 10 of 11 subjects and the k_2 values were higher in 7 of 11 subjects in Treatment B than in Treatment A. These results suggested that there was a shift in the absorption pattern between the two treatments, with a tendency towards a lower initial absorption followed by a more rapid second phase when subjects were pretreated with apple juice.

Lag times prior to the onset of the second phase of absorption were compared between Treatment A and Treatment B by paired t test. Although there was a trend for the lag time to be longer in Treatment B than in Treatment A, the effect was only of borderline significance ($0.1 > P > 0.05$).

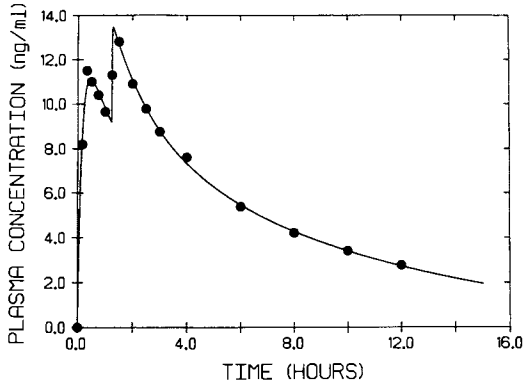

Fig. 2. Representative profile (subject 11) of serum levels of flurbiprofen after oral administration of an oral solution (Treatment C).

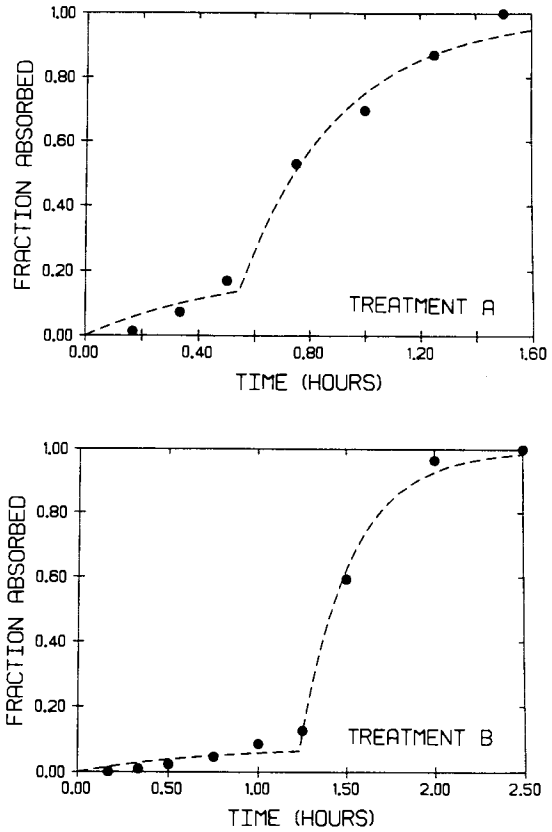

Fig. 3. Fraction absorbed as a function of time using the Loo–Riegelman analysis of data in Treatments A and B obtained in Subject 7.

Gastric Emptying Behavior and Relation to Lag Time

Figure 4 shows the gastric emptying times in Treatment A versus Treatment B. The gastric emptying time (as measured by the Heidelberg capsule technique) increased from a mean of 56.5 ± 37.2 (SD) min when water was given to 101.5 ± 17.1 min when apple juice was given ($P = 0.006$), excluding data from the two subjects who did not empty the capsule within 4 hr on both study days.

A plot of lag time for onset of the second phase of absorption vs gastric emptying time is presented in Fig. 5. Data from Subject 6, Treatment A, was excluded from this analysis, since almost all of the absorption was governed by the first rate constant ($F = 0.794$ by the k_1 absorption pathway). Figure 5 indicates that there is a significant correlation between the gastric emptying time of the Heidelberg capsule and the lag time for onset of the second phase of flurbiprofen absorption from immediate-release dosage forms ($r = 0.623$ and $0.01 > P > 0.001$).

DISCUSSION

When an oral dosage form is administered, the rate-limiting step in absorption will dictate the form of the observed absorption kinetics. At one end of the spectrum are sustained-release dosage forms, where the absorption kinetics should mirror the release kinetics from the dosage form. Zero-order kinetics are usually the aim and have been achieved *in vivo* by both osmotically driven devices and matrix release devices (11). At the other extreme, uptake by the intestinal mucosa is rate limiting. This is most likely to occur with compounds which are passively absorbed but are water soluble and have a low partition coefficient. For these drugs it may be expected that formulation and timing of the dose will have little effect on the observed absorption rate. Between the extreme cases of dosage form and mucosa domination of the absorption profile, there is a wide variation in the degree to which formulation, physiology, and permeability influence the kinetics of drug absorption.

Table I. Estimated Parameters and Measures of Fit After Treatment A[a]

Subject	F	k_1 (hr^{-1})	k_2 (hr^{-1})	t_0 (hr)	Measures of fit r^2	MSC
1	0.289	0.672	0.800	1.11	0.958	2.45
2	0.0476	2.92	2.93	0.244	0.973	2.00
3	0.458	0.956	0.238	0.364	0.975	3.25
4	0.643	0.625	1.51	0.500	0.987	3.61
5	0.261	0.369	1.65	1.42	0.997	5.07
6	0.794	0.366	1.58	2.03	0.994	4.63
7	0.226	1.71	2.88	0.544	0.988	3.25
8	0.0957	2.25	3.64	0.945	0.999	5.88
9	0.620	0.507	2.90	1.19	0.992	4.21
10	0.197	0.148	0.762	1.12	0.999	6.39
11	0.132	1.98	2.98	0.986	0.995	4.37
12	0.135	0.852	1.34	1.65	0.997	5.07
Mean	0.325	1.11	1.93	1.01	0.988	4.18
CV (%)	75.4	79.7	56.5	53.1	1.29	31.8
From mean FA	0.138	0.823	1.35	1.64	0.997	5.07

[a] k_1 and k_2 are the absorption rate constants for the successive absorption pathways, t_0 is the lag time before the second rate constant becomes operative, and F is the fraction of drug absorbed via pathway 1.

Table II. Estimated Parameters and Measures of Fit After Treatment B[a]

Subject	F	k_1 (hr^{-1})	k_2 (hr^{-1})	t_0 (hr)	Measures of fit r^2	MSC
1	0.186	0.460	1.72	1.09	0.998	5.45
2	0.110	0.793	20.02	1.99	0.997	4.97
3	0.578	0.323	12.77	1.47	0.979	3.40
4	0.0744	0.522	0.582	1.62	0.999	5.96
6	0.104	0.0789	0.737	1.50	0.9999	8.77
7	0.0792	1.32	3.42	1.23	0.997	4.97
8	0.251	1.49	6.13	1.23	0.999	5.67
9	0.423	3.04	1.10	1.40	0.996	4.86
10	0.0976	0.0883	0.748	1.44	0.999	7.03
11	0.262	0.112	1.65	0.909	0.997	4.88
12	0.0456	0.790	1.76	1.58	0.999	6.15
Mean	0.201	0.820	4.60	1.41	0.996	5.65
CV (%)	33.4	107.	136.	20.6	0.59	24.5
From mean FA	0.411	0.436	1.66	1.38	0.999	6.24

[a] See Table I, footnote *a*.

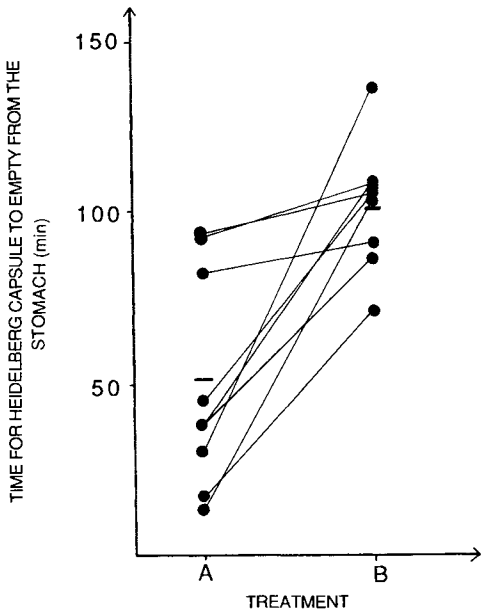

Fig. 4. Gastric emptying times of the Heidelberg capsule in the fed (Treatment B) and fasted (Treatment A) state.

One general factor that has often been identified as having significant influence on drug absorption is coadministration of the drug with a meal. Several reports have indicated that when certain drugs are administered orally in immediate-release dosage forms, their absorption is changed in the presence of food. In some cases it has been possible to link a specific aspect of the meal with the alteration in drug absorption. A classic example is the precipitation of tetracyclines with calcium ion in milk (12), leading to ineffective absorption. On the other hand, it has been shown that high-fat meals improve the absorption of griseofulvin (13) and increase the rate of absorption from certain theophylline dosage forms (14).

In yet other cases, changes in absorption may occur secondary to physiological changes associated with food intake. Eating has several effects on GI physiology that could influence drug absorption: the pH in the stomach is neutralized for a brief period (15,16), the gastric empting rate is reduced (17), and there are substantial gastric, biliary, and pancreatic secretions (18). Elevation of gastric pH has been demonstrated to affect adversely the absorption of weak bases such as ketoconazole (19), while it appears likely that bile salts enhance the dissolution and absorption of poorly soluble compounds.

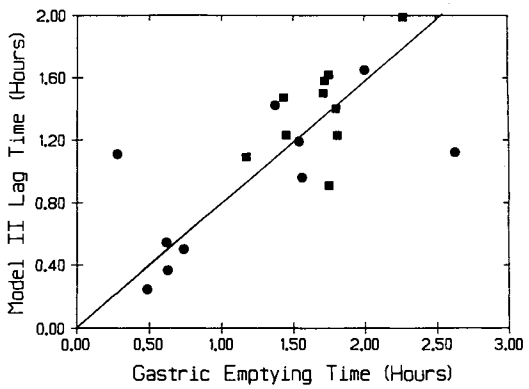

Fig. 5. Lag time for onset of flurbiprofen levels as a function of gastric emptying time for the Heidelberg capsule. Circles represent fasted-state data, while squares represent fed-state data.

The importance of gastric emptying in drug absorption has been studied for immediate-release dosage forms in the fasted state and for sustained-release dosage forms between the fed and the fasted state. Studies with ethanol (20–22) and acetaminophen (23) have explicitly demonstrated that gastric emptying can be rate controlling to the absorption of highly permeable drugs from immediate-release dosage forms in the fasting state. Additionally, the Nottingham group (24) has performed many gamma-scintigraphy studies showing that meal ingestion considerably prolongs the gastric residence time of monolithic sustained-release dosage forms.

Fed- vs Fasted-State Changes in Gastric Emptying Time and Lag Time

Apple juice administration resulted in a longer gastric emptying time than water and also in a tendency for the lag time prior to the onset of the second phase of absorption to be prolonged. The effect on the emptying time for the Heidelberg capsule was pronounced, with the capsule staying in the stomach an average of 45 min longer in the fed than the fasted state. When the difference in emptying time between the two treatments was small, this was because the emptying time in Treatment A was long, rather than because the emptying time in Treatment B was short. Considerable variability in the Heidelberg capsule emptying time in the fasted state (Treatment A) is expected, since this will depend on the timing of Heidelberg capsule administration relative to the occurrence of the next IMMC.

A perfect correlation between gastric emptying and lag times would not be expected for two reasons. First, the Heidelberg capsule, in most cases, requires passage of an IMMC in order to empty from the stomach, whereas solutions and suspensions may partially empty under less active motility conditions. This would lead to a longer time for the Heidelberg capsule to empty than for onset of k_2 contribution to flurbiprofen levels. On the other hand, the drug must travel to the absorptive sites and across the intestinal epithelia before it can be detected in the serum, which would tend to make the lag time longer than the gastric emptying times.

There was a significant correlation between the gastric emptying time of the Heidelberg capsule and the calculated lag times. This behavior is very similar to that observed for acetaminophen by Clements *et al.* (23) and suggests that gastric emptying is an important limitation to the absorption of flurbiprofen. Since gastric emptying can be quite variable between subjects and within the fed and fasted states, these results tend to suggest that variability in absorption of flurbiprofen can be attributed to intersubject and interday differences in physiology rather than variability in dosage form performance.

Disintegration Considerations

The longer lag times in the tablet treatments compared with the solution treatment could not be attributed to disin-

tegration problems; test tablets disintegrated in less than 2 min in either water or apple juice. However, settling of the dispersed dosage form appeared rapid and this was borne out by the assay results from a further disintegration study in which 200 ml of apple juice was warmed to 37°C in a beaker immersed in a water bath. A flurbiprofen tablet was placed in the beaker and allowed to disintegrate, a process that was completed within 2 min. The contents of the beaker were briefly stirred until the disintegrated particles were well dispersed, then the stirrer was removed. Samples were taken from a fixed location near the surface of the fluid upon removal of the stirrer and at 1, 2, and 5 min after removal. After 5 min, only one-fifth of the flurbiprofen was in solution or suspended in the apple juice, the rest remaining undissolved in the sediment. This behavior is consistent with the Treatment B results *in vivo*, where, in 9 of 11 instances, less than 30% of the flurbiprofen was absorbed according to k_1, with the rest being absorbed after the onset of the rapid absorption phase (see Table II).

Double-Peak Phenomenon

Flurbiprofen exhibited double-peak behavior in the majority of the oral solution studies. This was in contrast to work of Szpunar (2) in which little of this behavior was observed. A likely reason for the apparent difference in findings is that the Szpunar protocol called for fewer blood samples in the first 2 hr after administration. The incidence of double peaks in the flurbiprofen serum profiles supports the hypothesis that the drug may have gastric emptying limited absorption. Other drugs for which gastric emptying has been proposed to influence absorption and which exhibit double peak behavior include cimetidine (25,26) and acetaminophen (23). Penicillamine and veralipride also exhibit double-peak behavior when administered orally (8,27). As with the aforementioned compounds, double peaks occurred early in the absorption profile, suggesting that they were unrelated to enterohepatic cycling. Further, the frequency appeared to be dosage form dependent, occurring more frequently in the solution than in the tablet phases of the study. There are two theories regarding the early double-peak phenomenon. First, there may be two distinct absorption sites for the drug in the GI tract, separated by a region of relatively low absorption [e.g., Plusquellec's model (9)]. Second, for drugs whose absorption is limited by gastric emptying, biphasic emptying could result in biphasic absorption, albeit from the same major absorptive site [e.g., Clements' model (23)].

Interpretation of Model II

Taken together, the correlation between gastric emptying and the onset of the second phase of drug absorption, the disintegration test results, and the double-peak phenomena are strongly suggestive of a key role for gastric emptying in the absorption of flurbiprofen. In light of these results, the interpretation of Model II would be that part of the dose dissolves and empties slowly with the meal or the initially ingested water, while the rest sediments and remains in the stomach until the next IMMC activity, at which time it is emptied and rapidly absorbed.

Clinical Relevance

Overall, the extent of flurbiprofen absorption was similar whether it was administered as a solution or as a tablet, and in the fed and fasted states. The lag time for onset of the second phase of absorption from tablets appears to be significantly correlated with gastric emptying. Because there is significant variation in gastric emptying between individuals, the onset of action of flurbiprofen tablet formulations may likewise be expected to vary. In general, though, the second phase of absorption of flurbiprofen from tablets could be expected to result in therapeutic levels within about an hour of administration when the drug is given on an empty stomach. Delays in absorption would be expected to be more pronounced when the flurbiprofen dose is given in conjunction with meals. This effect may be exacerbated when the drug is coadministered with solid/liquid meals which are dense in calories and slow to empty from the stomach. Based on the data presented, one could also anticipate that, in patients with gastroparetic conditions, the onset of flurbiprofen absorption would be delayed.

Finally, it appears that the variability observed between subjects in the absorption profile of the solid dosage form more likely results from interindividual variation in gastric emptying behavior than from the formulation or the drug's physical characteristics.

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A program for Model II, pharmacokinetic parameters, and goodness-of-fit data for the oral solution phase are available upon request from the authors.

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