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Evaluation of an enteric coated naproxen tablet using gamma scintigraphy and pH monitoring

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Summary

Enteric coated naproxen tablets and pH-sensitive radiotelemetry capsules were both radiolabelled and administered to 6 healthy volunteers following breakfast. The median gastric emptying times for the tablets and capsules were 3.3 h and 4.2 h, respectively. In general, the intragastric pH remained below 2 with only transient increases following food consumption. Five of the naproxen tablets disintegrated in the small intestine and one in the stomach. In the ileum the pH was greater than 6 resulting in a mean time for tablet disintegration of 1.2 h after gastric emptying. There was a close correlation between tablet disintegration and the first detection of naproxen in the blood. Peak plasma concentrations of the drug occurred 4 h after tablet disintegration. This study has demonstrated that gastric emptying is the main factor influencing the onset of drug release from enteric coated tablets.

Introduction

Oral administration of anti-inflammatory drugs may result in adverse side effects such as gastrointestinal discomfort, nausea and gastric bleeding. The incidence of such reactions from naproxen can be reduced by dosing with enteric coated tablets (Trondstad et al., 1985). Such tablets are coated with a polymer designed to withstand the acid environment of the stomach but to dissolve readily once the tablets encounter the higher pH levels of the small intestine. Although this results in a delay in naproxen absorption, improved bioavailability can be achieved with enteric coated tablets compared with plain tablets (Gamst et al., 1984).

The principal factors likely to influence drug absorption from enteric coated naproxen tablets include: the gastric residence time, intestinal pH, and small intestinal transit. The presence of food in the stomach delays gastric emptying of tablets (Davis et al., 1986a) and can also result in increases in intragastric pH (Ovesen et al., 1986). Whilst gastric emptying is highly variable for tablets taken soon after a meal, small intestinal transit is relatively constant being typically 3–4 h (Davis et al., 1986b).

The present study was designed to evaluate the factors influencing the bioavailability of naproxen from an enteric coated tablet. A radiolabelled preparation was administered following a meal

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and gastrointestinal transit monitored using a gamma camera. Simultaneously the pH in the stomach and small intestine was recorded using a pH-sensitive radiotelemetry capsule, and blood specimens were obtained for drug analysis.

Materials and Methods

Tablet preparation

The tablets each contained 250 mg naproxen and 5 mg cation exchange resin powder radiolabelled with indium-111. They were compressed using a single punch tablet machine and had dimensions 12 × 7 × 5 mm. The experimental tablets were mixed with a batch of coloured, non-radioactive, naproxen tablets of the same size, and then coated with an aqueous acrylic resin dispersion in a fluid bed coater (Uniglatt). The radiolabelled tablets were then separated from the coloured tablets. The finished product complied with the European Pharmacopoeia tests for enteric coated tablets.

Subjects

Six healthy male volunteers, aged 19–23 years, participated. None was taking any medication, all were non-smokers and had abstained from alcohol for at least 2 days immediately prior to dosing.

The study was approved by the Medical School Ethical Committee and each subject provided written informed consent.

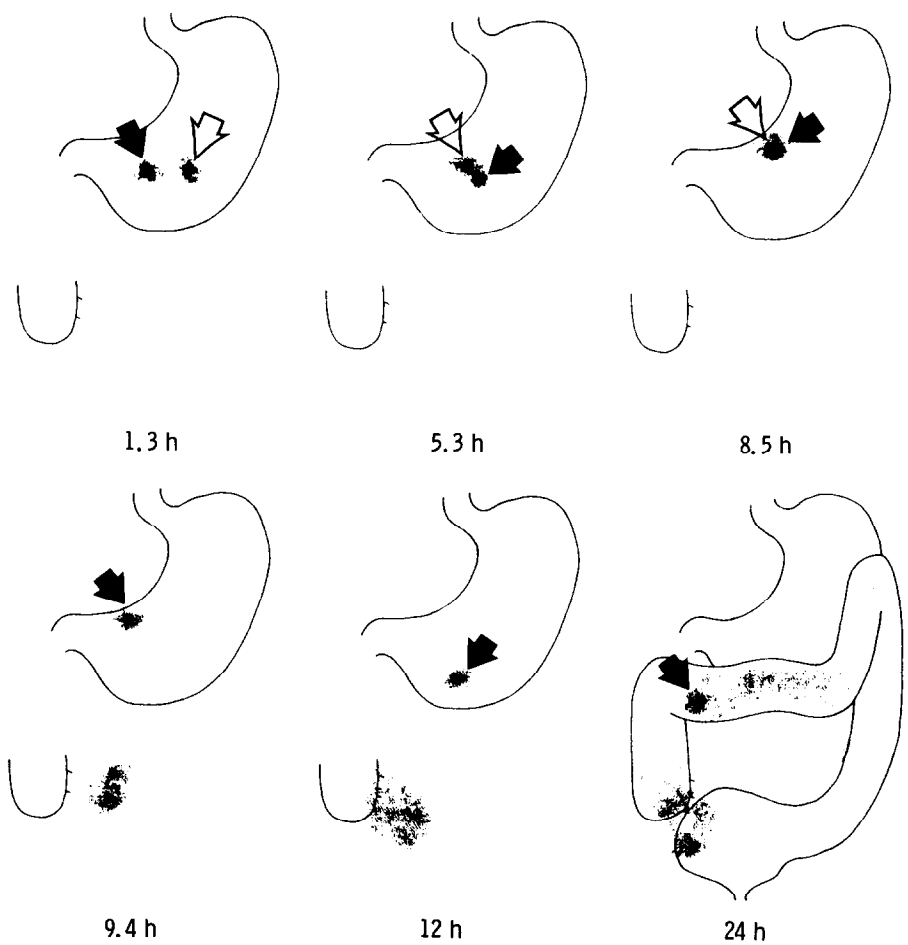

Fig. 1. Gastrointestinal transit of the naproxen tablet (⇧) and radiotelemetry capsule (⬆) in Subject 4.

Methods

After an overnight fast, at 08.45 h the subjects consumed a Scandinavian breakfast of one slice of ham and one slice of cheese on coarse bread with butter, 200 ml milk and two cups of tea. At 09.15 h each subject swallowed a naproxen tablet radiolabelled with 1 MBq indium-111, and a pH-sensitive radiotelemetry capsule (Remote Control Systems, London) radiolabelled with 1.5 MBq technetium-99m, along with 100 ml water containing 1.5 MBq ^{99m}Tc-labelled diethylenetriaminepentaacetic acid (Tc-DTPA).

Anterior images of the abdomen were obtained using a gamma camera. During the first 9 h after dosing, images were recorded at approximately 20 min intervals and from 9 to 12 h at hourly intervals. An additional image was recorded at 09.00 h the following day. During the study the subjects remained moderately active and were imaged standing. The indium and technetium images were obtained simultaneously but recorded separately by computer for subsequent analysis. The distribution of the Tc-DTPA outlined the stomach and colon and facilitated identification of the locations of the tablet and capsule in the images viewed on a television monitor (Fig. 1).

Food was provided for the volunteers. At 13.25 h each subject consumed a lunch of one slice of ham and two slices of cheese on coarse bread with butter, 200 ml milk and one cup of tea; and at 18.00 h an evening meal of fruit juice, grilled steak, chips and peas followed by cheesecake and coffee. Each subject also drank coffee at 11.10 h, 15.30 h and 20.20 h.

The pH-sensitive capsule consisted of a glass envelope 28 mm long by 7 mm diameter, containing a glass electrode, transmitter, mercury battery and self-contained reference cell. The capsules were calibrated in buffer solutions prior to administration. During the study signals were detected by an aerial worn around the waist, demodulated by a receiver (Remote Control Systems, London) and recorded on a multichannel pen recorder over the initial 12 h after dosing.

Venous blood samples were obtained immediately prior to dosing and following dosing at hourly intervals for 10 h, with additional specimens being taken at 5.5 h, 6.5 h, 12 h and 24 h. The plasma was stored frozen until being analysed for naproxen by spectrofluorometry.

Results

For each subject both the naproxen tablet and the radiotelemetry capsule were in the stomach at the time of recording the first image. The median times for gastric emptying of the tablets and capsules were 3.3 and 4.2 h, respectively (Table 1). In none of the subjects did the capsule leave the stomach before the tablet, but the differences in emptying rates were not significant ($P > 0.05$, paired t-test). In two subjects the radiotelemetry capsule remained in the stomach for more than 12 h. The small intestinal transit time for the naproxen preparation ranged from 1.5 to 6.4 h with a median time of 3.6 h.

In 5 of the subjects the tablet disintegrated in the small intestine, on average 1.2 h after leaving

TABLE 1

Gastric emptying times

Subject	Time (h)	
	Naproxen tablet	Radiotelemetry capsule
1	2.7	>12
2	3.9	4.5
3	3.0	3.8
4	8.9	>12
5	2.2	3.0
6	3.6	3.6
Median	3.3	4.2

TABLE 2

Tablet disintegration times

Subject	Time (h)	
	After dosing	After leaving stomach
1	4.2	1.5
2	5.0	1.1
3	1.6	
4	9.0	0.1
5	4.3	2.1
6	5.0	1.4
Mean	4.9	1.2

TABLE 3

Radiotelemetry capsule location and pH value

Time (h)	Subject					
	1	2	3	4	5	6
0.2	St 1.9	St < 1	St 1.2	St 2.1	St < 1	St 1.1
0.5	St 1.5	St < 1	St 1.2	St 2.4	St < 1	St < 1
1.0	St 1.0	St 1.2	St 1.2	St 2.4	St < 1	St < 1
1.5	St < 1	St 1.1	St 1.1	St 2.5	St 1.0	St 1.0
2.0	St 1.4	St < 1	St 1.7	St 2.1	St < 1	St 1.2
3.0	St < 1	St < 1	St < 1	St < 1	SI 8.0	St < 1
4.0	St < 1	St < 1	SI 6.8	St < 1	SI 7.8	SI 5.6
5.0	St 1.5	SI 4.4	SI 6.6	St 1.0	SI 9.2	SI 6.1
6.0	St 1.4	SI 6.0	SI 6.3	St 2.0	SI 9.5	SI 6.5
7.0	St 1.0	SI 6.8	SI 7.0	St < 1	SI 9.6	SI 6.1
8.0	St < 1	SI 6.9	SI 7.6	St < 1	SI 9.8	SI 6.0
9.0	St 1.9	SI 6.8	SI 7.6	St 2.4	SI 9.8	SI 5.8
10	St 1.5	AC 6.2	SI 7.6	St 1.5	SI 9.0	SI 5.8
11	St 1.5	AC 6.3	SI 7.4	St 1.0	Cae 7.5	SI 5.7
12	St 1.2	AC 6.2	SI 7.6	St < 1	Cae 7.7	Cae 4.9

Key: St = stomach; SI = small intestine; Cae = caecum; AC = ascending colon.

the stomach (Table 2). The remaining tablet (in Subject 3) began to disperse in the stomach 1.6 h after dosing. The preparation became widely dispersed in the large intestine in all the subjects.

The pH values in the stomach and intestine are listed in Table 3. Typically the pH in the stomach was less than 2 and in the ileum greater than 6. The pH in the caecum was about one pH unit less than in the terminal ileum. Increases in intragastric pH following breakfast and lunch were of short duration. The highest pH values in the stomach were recorded from Subject 4. Eating lunch caused an increase in pH from < 1 to a peak value of 6.5. The pH remained above 5 for only 6 min and within 1 h had fallen to 1.0. Although this subject recorded the highest intragastric pH, both following breakfast and lunch,

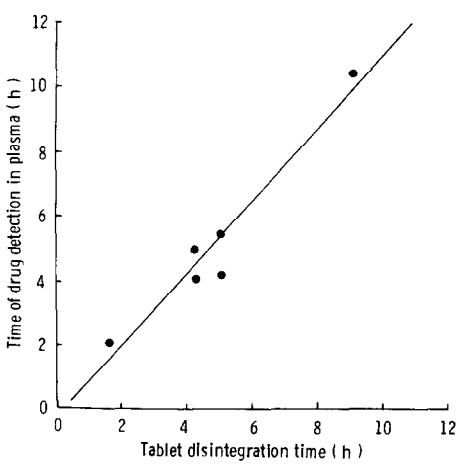

Fig. 2. Relationship between tablet disintegration and naproxen absorption ($r = 0.968$).

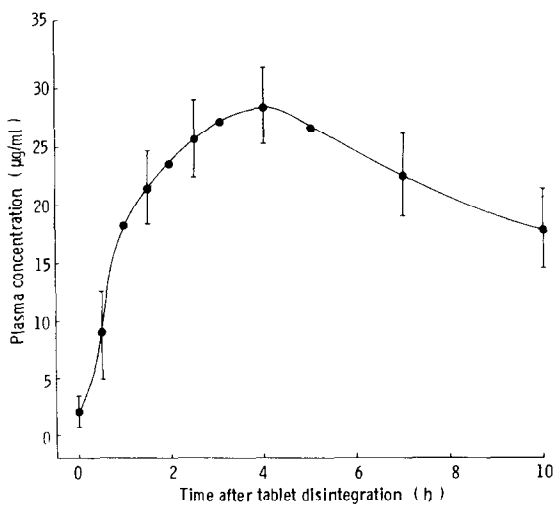

Fig. 3. Plasma concentration of naproxen (mean ± 1 S.E.M., $n = 6$).

the tablet remained intact throughout its 9 h residence in the stomach.

As shown in Fig. 2 there was a close correlation ($r = 0.968$) between tablet disintegration observed scintigraphically and the first detection of naproxen in the blood. The mean peak plasma naproxen concentration was 28 $\mu g \cdot ml^{-1}$ and occurred 4 h after tablet disintegration (Fig. 3). For each subject the peak plasma concentration of naproxen coincided with the transit of dispersed preparation into the colon. None of the subjects reported any adverse reactions resulting from the administration of the enteric coated preparation.

Discussion

The median times for gastric emptying of 3.3 h for the naproxen tablets and 4.2 h for the radiotelemetry capsules agree well with values reported previously for tablets taken after a meal (Davis et al., 1986a). It is not unusual in such circumstances for large non-disintegrating dosage forms to remain in the stomach for over 10 h (Davis et al., 1984). After leaving the stomach the naproxen preparation passed through the small intestine, on average in 3.6 h, in good agreement with data from other studies (Davis et al., 1986b).

The intragastric pH was rarely above 3 in any of the subjects and food consumption caused only transient increases. Once the radiotelemetry capsule had entered the small intestine a marked and rapid increase in pH was recorded. These findings are consistent with the observations of Ovesen et al. (1986) of a pH rise from about 3 to 6 on passing from the proximal to the distal duodenum. A comparison of pH readings from the radiotelemetry capsules with measurements on gastric aspirate has confirmed the reliability of the technique for monitoring during normal daily activities (Reynolds et al., 1986).

In 5 of the subjects the naproxen tablet disintegrated in the small intestine. The efficacy of the enteric coating was well demonstrated in Subject 4, in whom the tablet remained intact in the stomach for almost 9 h. The one tablet that disintegrated in the stomach did so relatively rapidly even though the intragastric pH remained low. This indicates that the coating may have been defective at the time of administration. There was a good correlation between the observation of tablet dispersion in the gamma camera images and the initial detection of naproxen in the plasma, thus validating the reliability of gamma scintigraphy for monitoring tablet behaviour in vivo. A previous study reported a lag time of 2 h for naproxen detection in the blood following administration of enteric coated tablets to fasted subjects (Gamst et al., 1984). These findings are consistent with a 0.8 h gastric residence (Davis et al., 1986a) plus 1.2 h for tablet disintegration in the small intestine as recorded in the present study.

The mean peak plasma naproxen concentration of 28 $\mu g \cdot ml^{-1}$ from the 250 mg tablet is in good agreement with the 53 $\mu g \cdot ml^{-1}$ reported following the administration of a 500 mg dose (Gamst et al., 1984). For individual subjects, the peak plasma concentration coincided with the transit of the preparation into the colon, indicating that the drug is principally absorbed from the small intestine.

Although the present study was undertaken in healthy young subjects, similar gastrointestinal transit rates have been reported for naproxen preparations in elderly volunteers (Davis et al., 1986a). Additionally, exercise has been shown to have no effect on small intestinal transit (Ollerenshaw et al., 1987), indicating that the results of studies during which subjects are only moderately active are applicable to normal daily situations.

Gastric emptying is the major factor influencing the rate of drug release from enteric coated tablets. In order to minimise variations in plasma concentrations, it may be appropriate to administer the tablet an hour before eating so as to reduce the likelihood of prolonged gastric retention.

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